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ACC/AHA TASK FORCE REPORT

ACC/AHA 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 (Committee on Management of Patients With Valvular Heart Disease)

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TABLE OF CONTENTS

Preamble
I. Introduction 1489
II. General Principles 1490
A. Evaluation of the Patient With a Cardiac Murmur 1490
1. Introduction 1490
2. Classification of Murmurs 1491
a. Dynamic Cardiac Auscultation 1492
b. Other Physical Findings 1492
c. Associated Symptoms 1492
d. Electrocardiography and Chest Roentgenography 1492
e. Echocardiography 1493
f. Cardiac Catheterization 1494
3. Approach to the Patient 1494
B. Endocarditis and Rheumatic Fever Prophylaxis 1495
1. Endocarditis Prophylaxis 1495
2. Rheumatic Fever Prophylaxis 1498
a. General Considerations 1498
b. Primary Prevention 1498
c. Secondary Prevention 1498
III. Specific Valve Lesions 1498
A. Aortic Stenosis 1498
1. Introduction 1498
a. Grading the Degree of Stenosis 1498
2. Pathophysiology 1499
3. Natural History 1499

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4. Management of the Asymptomatic Patient 1500
a. Initial Evaluation 1500
b. Serial Testing 1501
c. Medical Therapy 1501
d. Physical Activity and Exercise 1501
5. Indications for Cardiac Catheterization 1501
a. Low-Gradient Aortic Stenosis 1502
6. Indications for Aortic Valve Replacement 1502
a. Symptomatic Patients 1502
b. Asymptomatic Patients 1502
c. Patients Undergoing Coronary Artery Bypass Surgery 1502
7. Aortic Balloon Valvotomy 1503
8. Medical Therapy for the Inoperable Patient 1503
9. Evaluation After Aortic Valve Replacement 1503
10. Special Considerations in the Elderly 1504
B. Aortic Regurgitation 1504
1. Etiology 1504
2. Acute Aortic Regurgitation 1504
a. Pathophysiology 1504
b. Diagnosis 1504
c. Treatment 1505
3. Chronic Aortic Regurgitation 1505
a. Pathophysiology 1505
b. Natural History 1505
c. Diagnosis and Initial Evaluation of the Asymptomatic Patient 1508
d. Medical Therapy 1509
e. Physical Activity and Exercise 1511
f. Serial Testing 1511
g. Indications for Cardiac Catheterization 1512
h. Indications for Aortic Valve Replacement 1512
4. Concomitant Aortic Root Disease 1514
5. Evaluation of Patients After Aortic Valve Replacement 1514
6. Special Considerations in the Elderly 1514
C. Mitral Stenosis 1515
1. Pathophysiology and Natural History 1515
2. Evaluation and Management of the Asymptomatic Patient 1515
a. Initial Workup 1515
b. Medical Therapy: General 1517
c. Medical Therapy: Atrial Fibrillation 1518
d. Medical Therapy: Prevention of Systemic Embolization 1518
e. Recommendations Regarding Physical Activity and Exercise 1519
f. Serial Testing 1519
3. Evaluation of the Symptomatic Patient 1519
a. Initial Workup 1519
b. Indications for Cardiac Catheterization 1519
4. Indications for Surgical or Percutaneous Valvotomy 1521
5. Indications for Mitral Valve Replacement 1524
6. Management of Patients After Valvotomy or Commissurotomy 1524
7. Special Considerations 1525
a. Pregnant Patients 1525
b. Older Patients 1525
D. Mitral Valve Prolapse 1525
1. Pathophysiology and Natural History 1525
2. Evaluation and Management of the Asymptomatic Patient 1527
3. Evaluation and Management of the Symptomatic Patient 1528
4. Surgical Considerations 1529
E. Mitral Regurgitation 1530
1. Etiology 1530
2. Acute Severe Mitral Regurgitation 1530
a. Pathophysiology 1530
b. Diagnosis 1530
c. Medical Therapy 1530
3. Chronic Asymptomatic Mitral Regurgitation 1530
a. Pathophysiology 1530
b. Diagnosis 1531
c. Serial Testing 1531
d. Guidelines for Physical Activity and Exercise ..1531
e. Medical Therapy 1531
f. Indications for Cardiac Catheterization 1532
4. Indications for Surgery 1532
a. Types of Surgery 1532
b. Timing of Surgery for Symptomatic Patients With Normal Left Ventricular Function 1533
c. Timing of Surgery in Asymptomatic or Symptomatic Patients With Left Ventricular Dysfunction 1533
d. Asymptomatic Patients with Normal Left Ventricular Function 1534
e. Atrial Fibrillation 1534
f. Feasibility of Repair Versus Replacement 1535
5. Ischemic Mitral Regurgitation 1535
6. Evaluation of Patients After Mitral Valve Replacement or Repair 1535
7. Special Considerations in the Elderly 1535
F. Multiple Valve Disease 1535
1. Introduction 1535
2. Mixed Single Valve Disease 1536
a. Pathophysiology 1536
b. Diagnosis 1536
c. Management 1536
3. Combined Mitral Stenosis and Aortic Regurgitation 1537
a. Pathophysiology 1537
b. Management 1537
4. Combined Mitral Stenosis and Tricuspid Regurgitation 1537
a. Pathophysiology 1537
b. Diagnosis 1537
c. Management 1537
5. Combined Mitral and Aortic Regurgitation 1537
a. Pathophysiology 1537
b. Diagnosis and Therapy 1537
6. Combined Mitral and Aortic Stenosis 1537
a. Pathophysiology 1537
b. Diagnosis and Therapy 1537
7. Combined Aortic Stenosis and Mitral Regurgitation 1537
a. Pathophysiology 1537
b. Diagnosis and Therapy 1537
G. Tricuspid Valve Disease 1538
1. Pathophysiology 1538
2. Diagnosis 1538

3. Management 1538
H. Valvular Heart Disease Associated With Anorectic Drugs 1539

IV. Evaluation and Management of Infective Endocarditis 1541
A. Antimicrobial Therapy 1541
B. Culture-Negative Endocarditis 1544
C. Endocarditis in HIV-Seropositive Patients 1544
D. Indications for Echocardiography in Endocarditis 1544
E. Outpatient Treatment 1544
F. Indications for Surgery in Patients With Active Infective Endocarditis 1545

V. Management of Valvular Disease in Pregnancy 1545
A. Physiological Changes of Pregnancy 1545
B. Physical Examination 1546
C. Echocardiography 1546
D. General Management Guidelines 1546
E. Specific Lesions 1547
1. Mitral Stenosis 1547
2. Mitral Regurgitation 1547
3. Aortic Stenosis 1548
4. Aortic Regurgitation 1548
5. Pulmonary Valve Stenosis 1548
6. Tricuspid Valve Disease 1548
7. Marfan Syndrome 1548
F. Endocarditis Prophylaxis 1548
G. Cardiac Valve Surgery 1549
H. Anticoagulation 1549
1. Warfarin 1549
2. Heparin 1549

VI. Management of Valvular Heart Disease in Adolescents and Young Adults 1550
A. Aortic Stenosis 1550
B. Aortic Regurgitation 1552
C. Mitral Regurgitation 1552
D. Mitral Stenosis 1552
E. Tricuspid Valve Disease 1553
F. Pulmonic Stenosis 1554
1. Pathophysiology 1554
2. Diagnosis 1554
3. Clinical Course 1554
G. Pulmonary Regurgitation 1555

VII. Management of Patients With Prosthetic Heart Valves 1555
A. Classification of Prosthetic Heart Valves 1555
1. Mechanical Valves 1555
a. Ball Valves 1555
b. Disk Valves 1556
c. Bileaflet Valves 1556
2. Biological Valves 1556
a. Autograft Valves 1556
b. Autologous Pericardial Valves 1556
c. Homograft (or Allograft) Valves 1556
d. Porcine Heterograft (or Xenograft) Valves 1557
e. Bovine Pericardial Valves 1557
B. Complications of Prosthetic Heart Valves 1557
1. Guidelines for Reporting Clinical Results 1557
a. AATS/STS Guidelines for Clinical Reporting ..1557
2. Valve-Related Complications 1557
a. Major Randomized Trials 1558
C. Management of Patients With Prosthetic Heart Valves 1558
1. Antibiotic Prophylaxis 1558
a. Infective Endocarditis 1558
b. Recurrence of Rheumatic Carditis 1558
2. Antithrombotic Therapy 1558
a. Mechanical Valves 1558
b. Biological Valves 1559
c. Difficulties in Maintaining Anticoagulant Therapy 1560
d. Embolic Events During Adequate Antithrombotic Therapy 1560
e. Excessive Anticoagulation 1560
f. Antithrombotic Therapy in Patients Requiring Noncardiac Surgery/Dental Care 1560
g. Antithrombotic Therapy in Patients Needing Cardiac Catheterization/Angiography 1561
h. Thrombosis of Prosthetic Heart Valves 1561
3. Follow-up Visits 1562
a. First Outpatient Postoperative Visit 1562
b. Follow-up Visits in Patients Without Complications 1562
c. Follow-up Visits in Patients With Complications 1563
4. Reoperation to Replace a Prosthetic Valve 1563
D. Major Criteria for Valve Selection 1563

VIII. Evaluation and Treatment of Coronary Artery Disease in Patients With Valvular Heart Disease 1565
A. Probability of Coronary Artery Disease in Patients With Valvular Heart Disease 1565
B. Diagnosis of Coronary Artery Disease 1566
C. Treatment of Coronary Artery Disease at the Time of Aortic Valve Replacement 1566
D. Aortic Valve Replacement in Patients Undergoing Coronary Artery Bypass Surgery 1566
E. Management of Concomitant Mitral Valve Disease and Coronary Artery Disease 1567

ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease

Preamble

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the management or prevention of disease states. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably impact 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. Its charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. 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 specialty groups when appropriate. Writing groups 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 might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and cost-effectiveness.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of all the circumstances presented by that patient.

The Committee on Management of Patients With Valvular Heart Disease was chaired by Robert O. Bonow, MD, FACC, and included the following members: Blase Carabello, MD, FACC; Antonio C. de Leon, Jr., MD, FACC; L. Henry Edmunds, Jr., MD, FACC; Bradley J. Fedderly, MD, FAAFP; Michael D. Freed, MD, FACC; William H. Gaasch, MD, FACC; Charles R. McKay, MD, FACC; Rick A. Nishimura, MD, FACC; Patrick T. O'Gara, MD, FACC; Robert A. O'Rourke, MD, FACC; and Shahbudin H. Rahimtoola, MD, FACC. In August 1998, the full text of the guidelines was approved for publication in the November issue of the *Journal of the American College of Cardiology* and the executive summary for publication in the November 3 issue of *Circulation*. Reprints of both the full text and the executive summary are available from both organizations.

I. Introduction

The American College of Cardiology and the American Heart Association (ACC/AHA) have long been involved in the joint development of practice guidelines designed to assist physicians in the management of selected cardiovascular disorders or the selection of certain cardiovascular procedures. The determination of the disorders or procedures for which to develop guidelines is based on several factors, including importance to physicians 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 cardiological 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 Committee on Management of Patients With Valvular Heart Disease was given the task of reviewing and compiling this information base and making recommendations for diagnostic testing, treatment, and physical activity. For topics in which there is 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. Where no or few data exist, this is identified in the text.

The committee membership consisted of cardiovascular disease specialists as well as representatives of the cardiac surgery and family practice fields; both the academic and private practice sectors were represented. This document was reviewed by 3 outside reviewers nominated by the ACC and 3 outside reviewers nominated by the AHA, as well as numerous content reviewers and individuals nominated by the American Academy of Family Physicians and the Society of Thoracic Surgeons.

The guidelines follow the format established in previous

Abbreviations used in these guidelines:

AR	=	aortic regurgitation
AS	=	aortic stenosis
AVR	=	aortic valve replacement
CAD	=	coronary artery disease
ECG	=	electrocardiogram
LV	=	left ventricular
MR	=	mitral regurgitation
MS	=	mitral stenosis
MVP	=	mitral valve prolapse
MVR	=	mitral valve replacement
NYHA	=	New York Heart Association
TR	=	tricuspid regurgitation

ACC/AHA guidelines for classifying indications for diagnostic and therapeutic procedures:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is 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.

IIa. Weight of evidence/opinion is in favor of usefulness/efficacy.

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 and in some cases may be harmful.

The reference list is not exhaustive or all-inclusive, as this would be beyond the scope of this publication, but includes those papers that the committee believes represent the most comprehensive or convincing data and are necessary to support its conclusions.

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 Clinical Use of Cardiac Radionuclide Imaging (1), the Guidelines for Clinical Application of Echocardiography (2), the Guidelines for Exercise Testing (3), and the Guidelines for Coronary Angiography (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 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.

II. General Principles

A. Evaluation of the Patient With a Cardiac Murmur

1. Introduction. Cardiac auscultation remains the most widely used method of screening for heart disease. The production of murmurs is due to 3 main factors: (1) high blood flow rate through normal or abnormal orifices; (2) forward flow through a narrowed or irregular orifice into a dilated vessel or chamber; or (3) backward or regurgitant flow through an incompetent valve, septal defect, or patent ductus arteriosus. Often, several of these factors are 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 (eg, valvular aortic stenosis) 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. Two-dimensional (2-D) and Doppler echocardiography is particularly useful in this regard, as discussed in the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2). Diastolic murmurs virtually always represent pathological conditions and require further cardiac evaluation, as do most

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 or low-pitched diastolic murmurs
   b. Middiastolic murmurs
   c. Presystolic murmurs
3. Continuous murmurs

continuous murmurs. Continuous "innocent" murmurs include venous hums and mammary soufflés.

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 point in the cardiac cycle at which an adequate pressure difference between 2 chambers appears and disappears (5–9). A classification of cardiac murmurs is listed in Table 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 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 (eg, pregnancy, thyrotoxicosis, anemia, arteriovenous fistula), ejection of blood into a dilated vessel beyond the valve, or increased transmission of sound through a thin chest wall. Most benign innocent murmurs occurring in children and young adults are midsystolic and originate either from the aortic or pulmonic outflow tracts. Valvular or subvalvular obstruction (stenosis) of either ventricle may also cause a midsystolic murmur, the intensity depending in part on the velocity of blood flow across the narrowed area. Midsystolic murmurs also occur in certain patients with mitral regurgitation (MR) or, less frequently, tricuspid regurgitation (TR) resulting from papillary muscle dysfunction. Echocardiography is often necessary to separate a prominent and exaggerated (Grade 3 or greater) benign midsystolic murmur from one due to valvular aortic stenosis (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 occurring in the absence of pulmonary hypertension and in other 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 ischemia or infarction of the mitral papillary muscles or to their dysfunction due to LV dilatation. 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 immediate 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 pitch, 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.

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 in patients with ventricular septal defect or patent ductus arteriosus, and across the normal tricuspid valve in patients with atrial septal defect. In severe, long-term AR, a low-pitched diastolic murmur (Austin-Flint murmur) is often present at the LV apex; it may be either middiastolic or presystolic.

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).

a. Dynamic Cardiac Auscultation. Attentive cardiac auscultation during dynamic changes in cardiac hemodynamics often enables the careful observer to deduce the correct origin and

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. Following 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 (eg, PS, MS) become louder with both isotonic and submaximal isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise. However, the murmur of HCM often decreases with near-maximum 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 prompt 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 prompt squatting.
Postventricular premature beat or atrial fibrillation
Murmurs originating at normal or stenotic semilunar valves increase in intensity during the cardiac cycle following 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 following amyl nitrite inhalation, murmurs of MR, VSD, and AR decrease, while 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.

Abbreviations: AF = 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, VSD = ventricular septal defect.

significance of a cardiac murmur (10–13). Changes in the intensity of heart murmurs during various maneuvers are indicated in Table 2.

b. 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 (Figure 1). For example, a right heart murmur in early to midsystole at the lower left sternal border likely represents TR without pulmonary hypertension in an intravenous drug user who presents with fever, petechiae, Osler's node, and Janeway lesion.

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 left sternal border during expiration usually denotes pulmonic valve stenosis. LV dilatation on precordial palpation and bibasilar pulmonary rales favor the diagnosis of 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 upper intercostal spaces. The typical pulsus parvus and tardus may be absent in the elderly, even with severe AS secondary to the effects of aging on the vasculature. Pulsus parvus may also occur with severely low output from any cause. Factors that aid in the diagnosis of LV outflow tract obstruction are listed in Table 3.

c. Associated Symptoms. An important consideration in a patient with a cardiac murmur is the presence or absence of symptoms (14) (Figure 1). For example, symptoms of syncope, angina pectoris, or congestive heart failure in a patient with a midsystolic murmur will usually result in a more aggressive approach than in patients with a similar midsystolic murmur who have none of these symptoms. 2-D and Doppler echocardiography to rule in or out the presence of significant AS will likely be obtained. A history of thromboembolism or possible infective endocarditis will also usually result in a more extensive workup. In patients with cardiac murmurs and clinical findings suggestive of endocarditis, 2-D and Doppler echocardiography is usually indicated (2).

Conversely, many asymptomatic children and young adults with grade 2/6 midsystolic murmurs and no other cardiac physical findings need no further cardiac workup after the initial history and physical examination (Figure 1). A particularly important group is the large number of asymptomatic elderly patients, many with systemic hypertension, who have midsystolic murmurs related to sclerotic aortic valve leaflets; flow into tortuous, noncompliant great vessels; or a combination of these. Such murmurs must be distinguished from those caused by mild to severe valvular AS, which is prevalent in this age group. The absence of LV hypertrophy on electrocardiography is reassuring, and this test is considerably less costly than routine echocardiography.

d. 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 electrocardiogram (ECG) and chest x-ray are readily available and may have been obtained already. The absence of ventricular hypertrophy, atrial abnormality, arrhythmias, conduction abnormalities, prior myocardial infarction, and evidence of active ischemia on the ECG provides useful negative information at a relatively low cost. Abnormal findings on the ECG, such as ventricular hypertrophy or a prior infarction, should lead to a more extensive evaluation including 2-D and Doppler echocardiography (Figure 1).

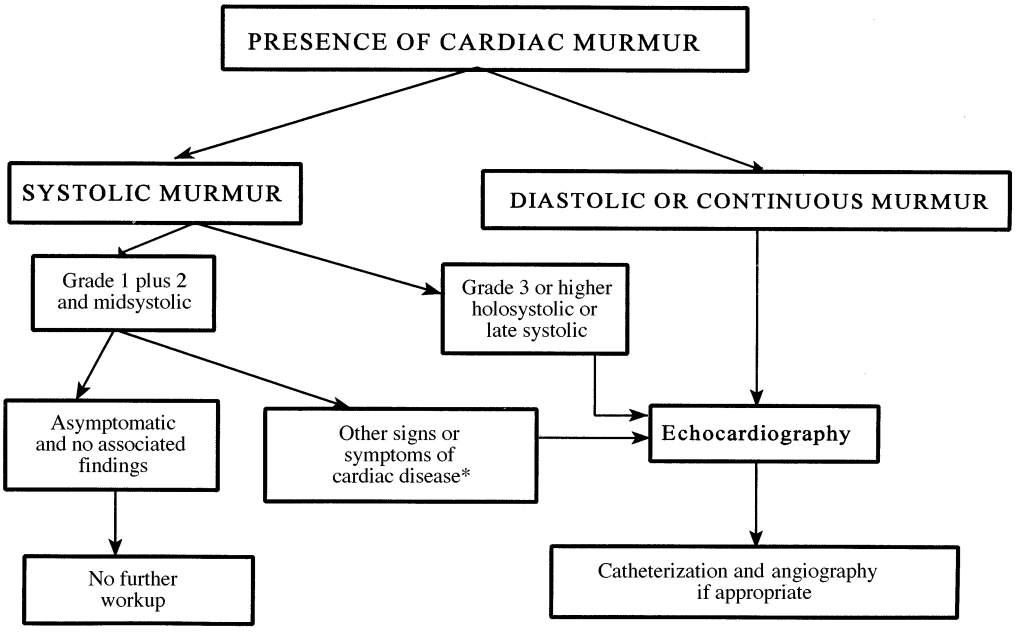

Figure 1. Strategy for evaluating heart murmurs. *If an ECG or chest x-ray has been obtained and is abnormal, an echocardiogram is recommended.

Posteroanterior and lateral chest roentgenograms often yield qualitative information on cardiac chamber size, pulmonary blood flow, pulmonary venous pressures, pulmonary vascular redistribution, and cardiac calcification in patients with cardiac murmurs. When abnormal findings are present on chest x-ray, 2-D and Doppler echocardiography should be performed (Figure 1). A normal chest x-ray and ECG are likely in patients with insignificant midsystolic cardiac murmurs, particularly in younger age groups and when the murmur is less than grade 3 in intensity (15–17). Many asymptomatic patients need neither an ECG nor a chest x-ray when a careful cardiac examination indicates an insignificant vibratory midsystolic heart murmur and no other abnormal findings.

e. Echocardiography. Echocardiography is an important noninvasive method for assessing the significance of cardiac murmurs by imaging cardiac structure and function and the direction and velocity of blood flow through cardiac valves and chambers. 2-D echocardiography may indicate abnormal valvular motion and morphology but usually does not indicate the severity of valvular stenosis or regurgitation except in MS. With Doppler echocardiography, a change or shift in ultrasound frequency indicates the direction and velocity of flow in relation to transducers. The direction of flow is displayed as a spectral velocity profile of blood flowing toward or away from the transducer. The velocity reflects the pressure gradient across stenotic and regurgitant valves. The presence of an abnormal regurgitant jet on color flow imaging detects valvular regurgitation and provides semiquantitative information about its severity.

Although 2-D echocardiography and color flow Doppler imaging can provide important information on patients with

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

	Valvular	Supravalvular	Discrete Subvalvular	HOCM
Valve calcification	Common after age 40	No	No	No
Dilated ascending aorta	Common	Rare	Rare	Rare
PP after VPB	Increased	Increased	Increased	Decreased
Valsalva effect on SM	Decreased	Decreased	Decreased	Increased
Murmur of AR	Common	Rare	Sometimes	No
Fourth heart sound (S_4)	If severe	Uncommon	Uncommon	Common
Paradoxic 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. Abbreviations: AR = aortic regurgitation, HOCM = hypertrophic obstructive cardiomyopathy, LIS = left intercostal space, PP = pulse pressure, RIS = right intercostal space, SM = systolic murmur, VPB = ventricular premature beat. From Marriott HJL. Bedside Cardiac Diagnosis. Philadelphia, PA: JB Lippincott Co; 1993:116. With permission.

cardiac murmurs, these tests are not necessary for all patients with cardiac murmurs and usually add little but expense in the evaluation of asymptomatic patients with short grade 1 to 2 midsystolic murmurs and otherwise normal physical findings. Alternatively, if the diagnosis is still questionable after transthoracic echocardiography, transesophageal echocardiography or cardiac catheterization may be appropriate.

It is important to consider that many recent studies indicate that Doppler ultrasound devices are very sensitive and may detect valvular regurgitation through the tricuspid and pulmonic valves in a large percentage of young, healthy subjects and through left-sided valves (particularly the mitral) in a variable but lower percentage (18–22).

General recommendations for performing 2-D and Doppler echocardiography in asymptomatic and symptomatic patients with heart murmurs follow. Of course, individual exceptions to these indications may exist.

Recommendations for Echocardiography in Asymptomatic Patients With Cardiac Murmurs

Indication	*Class*
1. Diastolic or continuous murmurs.	I
2. Holosystolic or late systolic murmurs.	I
3. Grade 3 or midsystolic murmurs.	I
4. Murmurs associated with abnormal physical findings on cardiac palpation or auscultation.	IIa
5. Murmurs associated with an abnormal ECG or chest x-ray.	IIa
6. Grade 2 or softer midsystolic murmur identified as innocent or functional by an experienced observer.	III
7. To detect "silent" AR or MR in patients without cardiac murmurs, then recommend endocarditis prophylaxis.	III

Recommendations for Echocardiography in Symptomatic Patients With Cardiac Murmurs

Indication	*Class*
1. Symptoms or signs of congestive heart failure, myocardial ischemia, or syncope.	I
2. Symptoms or signs consistent with infective endocarditis or thromboembolism.	I
3. Symptoms or signs likely due to noncardiac disease with cardiac disease not excluded by standard cardiovascular evaluation.	IIa
4. Symptoms or signs of noncardiac disease with an isolated midsystolic "innocent" murmur.	III

f. 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 provides additional information on some patients in whom there is a discrepancy between echocardiographic and clinical findings. Indications for cardiac catheterization for hemodynamic assessment of specific valve lesions are given in sections III.A. through III.F. of these guidelines. Specific indications for coronary arteriography to assess the presence of coronary disease are given in section VIII.

3. Approach to the Patient. The evaluation of the patient with a heart murmur may vary greatly, depending on many of the considerations discussed above (17,23). These include the intensity of the cardiac murmur, its timing 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 whether other cardiac or noncardiac physical findings suggest that the cardiac murmur is clinically significant (Figure 1).

Patients with definite diastolic heart murmurs or continuous murmurs not due to a cervical venous hum or a mammary soufflé during pregnancy are candidates for 2-D and Doppler echocardiography. If the results of echocardiography indicate significant heart disease, further evaluation may be indicated. An echocardiographic examination is also recommended for most 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 cardiac diagnosis (eg, hypertrophic cardiomyopathy).

More specifically, further evaluation including echocardiography is 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 cardiomyopathy or mitral valve 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 following a premature ventricular contraction or after a long R-R interval in patients with atrial fibrillation. The diagnosis of MR or ventricular septal defect is likely.

In many patients with grade 1 to 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 to 2 midsystolic murmurs, including patients with symptoms or signs consistent with infective endocarditis or thromboembolism and those with symptoms or signs consistent with congestive heart failure, myocardial ischemia, or syncope. Echocardiography also usually provides an accurate diagnosis in patients with other abnormal physical findings on cardiac palpation or auscultation, the latter including widely split second heart sounds, systolic ejection sounds, and specific changes in intensity of the systolic murmur during certain physiological maneuvers as described in Table 2.

Although 2-D and Doppler echocardiography is an important test for those with a moderate to high likelihood of a

clinically important cardiac murmur, it must be reemphasized that 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 and includes many patients who have no heart murmur at all (18–22). This must be considered when the results of echocardiography are used to guide decisions concerning asymptomatic patients in whom echocardiography was used to assess the clinical 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.

Many murmurs in asymptomatic adults are innocent and have no functional significance. Such murmurs have the following characteristics: (1) grade 1 to 2 intensity at the left sternal border; (2) a systolic ejection pattern; (3) normal intensity and splitting of the second heart sound; (4) no other abnormal sounds or murmurs; and (5) no evidence of ventricular hypertrophy or dilatation and the absence of increased murmur intensity with the Valsalva maneuver (10). Such murmurs are especially common in high-output states such as pregnancy (24,25). 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 (17). 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 (1) define the primary lesion in terms of etiology and severity; (2) define hemodynamics; (3) define coexisting abnormalities; (4) detect secondary lesions; (5) evaluate cardiac chamber size and function; (6) establish a reference point for future comparisons; and (7) reevaluate the patient after an intervention.

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 etiology and severity of lesions, particularly in elderly patients.

B. Endocarditis and Rheumatic Fever Prophylaxis

1. Endocarditis Prophylaxis. Endocarditis is a serious illness associated with significant mortality. Its prevention by appropriate administration of antibiotics before procedures expected to produce bacteremia merits serious consideration. Experimental studies suggest that endothelial damage leads to platelet and fibrin deposition and thus a nonbacterial thrombotic endocardial lesion. In the presence of bacteremia, the organisms adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infective vegetation (26,27). Valvular and congenital abnormalities, especially those that result in abnormal high-velocity jet streams, can damage the endothelial lining and predispose to platelet aggregation and fibrin deposition at those sites, which are thus at higher risk for bacterial colonization.

Several issues must be considered in generating recommendations for endocarditis prophylaxis (28). Evidence supporting prophylaxis consists of the following:

Recommendations for Endocarditis Prophylaxis

Indication	*Class*
High-Risk Category	**I**
· Prosthetic heart valves, including bioprosthetic homograft and allograft valves.	
· Previous bacterial endocarditis.	
· Complex cyanotic congenital heart disease, (eg, single ventricle states, transposition of the great arteries, tetralogy of Fallot).	
· Surgically constructed systemic-pulmonary shunts or conduits.	
Moderate-Risk Category	**I**
· Most other congenital cardiac malformations (other than above or below).	
· Acquired valvular dysfunction (eg, rheumatic heart disease).	
· Hypertrophic cardiomyopathy.*	
· MVP with auscultatory evidence of valvular regurgitation and/or thickened leaflets.†	
Low- or Negligible-Risk Category	**III**
· Isolated secundum atrial septal defect.	
· Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua >6 mo).	
· Previous coronary artery bypass graft surgery.	
· MVP without valvular regurgitation.†	
· Physiological, functional, or innocent heart murmurs.‡	
· Previous Kawasaki disease without valvular dysfunction.	
· Cardiac pacemakers and implanted defibrillators.	

Adapted from Dajani et al (36) with permission.

***This committee recommends prophylaxis in hypertrophic cardiomyopathy only when there is latent or resting obstruction.**

†Patients with MVP without regurgitation require additional clinical judgment. Indications for antibiotic prophylaxis in MVP are discussed in section III.D.2. of these guidelines. Patients who do not have MR but do have echocardiographic evidence of thickening and/or redundancy of the valve leaflets and especially men ≥45 years may be at increased risk for bacterial endocarditis (36). Additionally, approximately one third of patients with MVP without MR at rest may have exercise-induced MR (37). Some patients may exhibit MR at rest on 1 occasion and not on others. There are no data available to address this latter issue, and at present, the decision must be left to clinical judgment, taking into account the nature of the invasive procedure, the previous history of endocarditis, and the presence or absence of valve thickening and/or redundancy.

‡In patients with echocardiographic evidence of physiological MR in the absence of a murmur and with structurally normal valves, prophylaxis is not recommended. The committee also does NOT recommend prophylaxis for physiological tricuspid and pulmonary regurgitation detected by Doppler in the absence of a murmur, as such findings occur in a large number of normal individuals and the risk of endocarditis is extremely low. Recommendations regarding Doppler echocardiography for purposes of antibiotic prophylaxis in patients who have received anorectic drugs are given in section III.H. of these guidelines.

Table 4. Endocarditis Prophylaxis for Dental Procedures (36)

A. Endocarditis prophylaxis recommended
· Dental extractions
· Periodontal procedures, including surgery, scaling and root planing, probing, recall maintenance
· Dental implant placement and reimplantation of avulsed teeth
· Endodontic (root canal) instrumentation or surgery only beyond the apex
· Subgingival placement of antibiotic fibers/strips
· Initial placement of orthodontic bands but not brackets
· Intraligamentary local anesthetic injections*
· Prophylactic cleaning of teeth or implants where bleeding is anticipated
B. Endocarditis prophylaxis not recommended
· Restorative dentistry† (operative and prosthodontic) with/without retraction cord
· Local anesthetic injections (nonintraligamentary)*
· Intracanal endodontic treatment; postplacement and buildup
· Placement of rubber dams
· Postoperative suture removal
· Placement of removable prosthodontic/orthodontic appliances
· Taking of oral impressions
· Fluoride treatments
· Taking of oral radiographs
· Orthodontic appliance adjustment
· Shedding of primary teeth

*Intraligamentary injections are directed between the root and bone to deliver anesthetic agents to the periosteum of the bone.

†Includes filling cavities and replacement of missing teeth. In selected circumstances, especially with significant bleeding, antibiotic use may be indicated. From Dajani et al (36) with permission.

Table 5. Endocarditis Prophylaxis for Nondental Procedures (36)

A. Endocarditis prophylaxis recommended
Respiratory tract
· Tonsillectomy/adenoidectomy
· Surgical operations involving respiratory mucosa
· Bronchoscopy with rigid bronchoscope
Gastrointestinal tract (prophylaxis for high-risk patients; optimal for moderate risk)
· Sclerotherapy for esophageal varices
· Esophageal stricture dilation
· Endoscopic retrograde cholangiography with biliary obstruction
· Biliary tract surgery
· Surgical operations involving intestinal mucosa
Genitourinary tract
· Prostatic surgery
· Cystoscopy
· Urethral dilation
B. Endocarditis prophylaxis not recommended
Respiratory tract
· Endotracheal intubation
· Bronchoscopy with a flexible bronchoscope, with or without biopsy*
· Tympanostomy tube insertion
Gastrointestinal tract
· Transesophageal echocardiography*
· Endoscopy with or without gastrointestinal biopsy*
Genitourinary tract
· Vaginal hysterectomy*
· Vaginal delivery*
· Caesarean section
· In uninfected tissue:
Urethral catheterization
Uterine dilation and curettage
Therapeutic abortion
Sterilization procedures
Insertion or removal of intrauterine devices
Other
· Cardiac catheterization, including balloon angioplasty
· Implantation of cardiac pacemakers, implantable defibrillators, and coronary stents
· Incision or biopsy of surgically scrubbed skin
· Circumcision

*Prophylaxis is optional for high-risk patients. From Dajani et al (36) with permission.

1. Clinical experience documents endocarditis following bacteremia.
2. Bacteremia by organisms known to produce endocarditis follows various procedures such as dental procedures, endoscopy, cystoscopy, etc.
3. Antibiotics to which known offending organisms are sensitive are available.
4. In laboratory animal models of endocarditis, antibiotic prophylaxis has been shown to be effective.
5. Small clinical studies in humans appear to show benefit from prophylaxis against endocarditis (29,30).

The following evidence raises questions about the value of prophylaxis:

1. Lack of any sufficiently large, controlled clinical trials to support the application of the results of laboratory animal studies to humans.
2. Clinical reports of failure of antibiotic prophylaxis against endocarditis (28,31) or studies that appear to show that prophylaxis is not protective (32).
3. The evidence that dental and other procedures cause endocarditis is circumstantial. With the incidence of bacteremia (positive blood culture) varying from 8% (urethral catheterization) to as high as 88% (periodontal surgery) (33), the actual incidence of endocarditis is low (10 to 60 cases/1 million persons per year) (28).
4. In specific circumstances, such as prophylaxis for all cases of MVP, the risk of death from penicillin prophylaxis is estimated to be greater than the risk for infective endocarditis (34,35).

In view of these issues, it has been suggested that the risk of endocarditis in patients with preexisting cardiac disorders be classified as relatively high, moderate, and low or negligible, as determined by the cardiac disorder. Guidelines for the prevention of endocarditis have been issued by the American Heart Association (36), and the recommendations made here are based on those guidelines.

Various dental and/or surgical procedures are associated with varying degrees and frequencies of bacteremia. The frequency of bacteremia is highest with dental and oral proce-

Table 6. Endocarditis Prophylaxis Regimens for Dental, Oral, Respiratory Tract, or Esophageal Procedures (36)

Situation	Agent	Regimen*
Standard general prophylaxis	Amoxicillin	Adults: 2.0 g; children: 50 mg/kg PO 1 h before procedure.
Unable to take oral medication	Ampicillin	Adults: 2.0 g IM or IV; children: 50 mg/kg IM or IV within 30 min before procedure.
Penicillin-allergic	Clindamycin or	Adults: 600 mg; children: 20 mg/kg PO 1 h before procedure.
	Cephalexin† or cephadroxil† or	Adults: 2.0 g; children 50 mg/kg PO 1 h before procedure.
	Azithromycin or clarithromycin	Adults: 500 mg; children 15 mg/kg PO 1 h before procedure.
Penicillin-allergic and unable to take oral medications	Clindamycin or	Adults: 600 mg; children 20 mg/kg IV within 30 min before procedure.
	Cefazolin†	Adults: 1.0 g; children: 25 mg/kg IM or IV within 30 min before procedure.

*Total children's dose should not exceed adult dose.

†Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins. From Dajani et al (36) with permission.

Table 7. Endocarditis Prophylaxis Regimens for Genitourinary/Gastrointestinal (Excluding Esophageal) Procedures (36)

Situation	Agent(s)*	Regimen†
High-risk patients	Ampicillin plus gentamicin	Adults: ampicillin 2.0 g IM/IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting the procedure. Six hours later, ampicillin 1 g IM/IV or amoxicillin 1 g PO. Children: ampicillin 50 mg/kg IM or IV (not to exceed 2.0 g) plus gentamicin 1.5 mg/kg within 30 min of starting the procedure. Six hours later, ampicillin 25 mg/kg IM/IV or amoxicillin 25 mg/kg PO.
High-risk patients allergic to ampicillin/amoxicillin	Vancomycin plus gentamicin	Adults: vancomycin 1.0 g IV over 1–2 h plus gentamicin 1.5 mg/kg IV/IM (not to exceed 120 mg). Complete injection/infusion within 30 min of starting the procedure. Children: vancomycin 20 mg/kg IV over 1–2 h plus gentamicin 1.5 mg/kg IV/IM. Complete injection/infusion within 30 min of starting the procedure.
Moderate-risk patients	Amoxicillin or ampicillin	Adults: amoxicillin 2.0 g PO 1 h before procedure, or ampicillin 2.0 g IM/IV within 30 min of starting the procedure. Children: amoxicillin 50 mg/kg PO 1 h before procedure, or ampicillin 50 mg/kg IM/IV within 30 min of starting the procedure.
Moderate-risk patients allergic to ampicillin/amoxicillin	Vancomycin	Adults: vancomycin 1.0 g IV over 1–2 h. Complete infusion within 30 min of starting the procedure. Children: vancomycin 20 mg/kg IV over 1–2 h. Complete infusion within 30 min of starting the procedure.

*No second dose of vancomycin or gentamicin is recommended.

†Total children's dose should not exceed adult dose. From Dajani et al (36) with permission.

Table 8. Primary Prevention of Rheumatic Fever (40)

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

From Dajani et al (40) with permission.

Table 9. Secondary Prevention of Rheumatic Fever (40)

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

Abbreviations: Pts = patients. *High-risk patients include patients with residual rheumatic carditis as well as patients from economically disadvantaged populations. From Dajani et al (40) with permission.

dures, intermediate with procedures involving the genitourinary tract, and lowest with gastrointestinal diagnostic procedures (28). Recommendations for endocarditis prophylaxis, as determined by dental, surgical, and other procedures, are listed in Tables 4 through 7.

The procedure—thus the portal of entry—is a determinant of the type of organism involved in the resulting bacteremia. This is usually the determinant of the antibiotic chosen for prophylaxis. Because streptococci are normal inhabitants of the oral cavity, the antibiotic prophylaxis regimen for dental and oral procedures is directed against these organisms. For genitourinary and lower gastrointestinal procedures, the antibiotic prophylactic regimen is designed to cover enterococci and other gram-negative organisms.

2. Rheumatic Fever Prophylaxis. *a. 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 (38,39). With the enhanced understanding of the causative organism, group A streptococcus, their rheumatogenicity is attributed to the prevalence of M protein serotypes in the offending organism. This has resulted in the development of kits that allow rapid detection of group A streptococci with specificity ≥95% and more rapid identification of their presence in upper respiratory infection. Because the test has a low sensitivity, the negative test requires a throat culture confirmation (39). Prompt recognition and treatment represent primary rheumatic fever prevention. For patients who have had a previous episode of rheumatic fever, continuous antistreptococcal prophylaxis results in secondary prevention.

b. Primary Prevention. Rheumatic fever prevention treatment guidelines have been established by the American Heart Association (40) (Table 8).

c. Secondary Prevention. 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 MS) should have prophylaxis for recurrent rheumatic fever. The AHA guidelines for secondary prevention are shown in Table 9. The AHA guidelines for duration of secondary prevention are shown in Table 10.

III. Specific Valve Lesions

A. Aortic Stenosis

1. Introduction. The most common cause of AS in adults is a degenerative-calcific process that produces an immobilization of the aortic valve cusps. This calcific disease progresses from the base of the cusps to the leaflets, eventually causing a reduction in the effective valve area; true commissural fusion may not occur. 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 VI.A. of these guidelines. Over several decades, progressive fibrosis and calcification of the congenitally abnormal valve (often bicuspid) produce a deformity that resembles the degenerative-calcific lesion. Rheumatic fever results in AS due to fusion of the commissures with scarring and eventual calcification of the cusps. Thus, calcification is a common feature of AS in older adults regardless of the primary cause (41–43).

An ejection systolic murmur may be heard in the presence of a normal valve, one that is thickened and minimally calcified, and one that is stenotic (41,44). The 3 conditions must be distinguished.

a. Grading the Degree of Stenosis. The aortic valve area must be reduced to one fourth its normal size before significant changes in the circulation occur. Because the orifice area of the normal adult valve is ≈3.0 to 4.0 cm^2, an area >0.75 to 1.0 cm^2 is usually not considered severe AS (44,45). Historically, the definition of severe AS is based on the hydraulic orifice-area formulae developed by Gorlin and Gorlin, which indicate that large pressure gradients accompany only modest increments in flow when the valve area is <0.75 cm^2 (46). However, in large

Table 10. Duration of Secondary Rheumatic Fever Prophylaxis (40)

Category	Duration
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	≥10 y 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, ie, teachers, day-care workers. From Dajani et al (40) with permission.

patients, a valve area of 1.0 cm^2 may be severely stenotic, whereas a valve area of 0.7 cm^2 may be adequate for a smaller patient.

On the basis of a variety of hemodynamic and natural history data, in these guidelines we graded the degree of AS as mild (area >1.5 cm^2), moderate (area >1.0 to 1.5 cm^2), or severe (area ≤1.0 cm^2) (46a). When stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally >50 mm Hg. 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 usually the primary determinant of the need for aortic valve replacement (AVR).

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 (47–49). 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 (50). 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 (50–52). The depressed contractile state of the myocardium may also be responsible for a low ejection fraction, but a combination of excessive afterload and depressed contractility contributes to a low ejection fraction in many patients (53). 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 (54).

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 (55–58). Thus, increased end-diastolic pressure usually reflects diastolic dysfunction rather than systolic dysfunction or failure (59). 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 (60). 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 (61,62). 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 mortalities than are seen in the absence of hypertrophy (63–65). Another problem that is particularly common in elderly patients, especially women, is an excessive or inappropriate degree of hypertrophy; wall thickness is greater than necessary to counterbalance the high intracavitary pressures (66–69). As a result, systolic wall stress is low, ejection fraction is high, and the ventricle resembles that seen in patients with hypertensive hypertrophic cardiomyopathy of the elderly (70). Such inappropriate LV hypertrophy has been associated with high perioperative morbidity and mortality (66,68).

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 hemodynamic studies performed largely in patients with moderate AS (71). Cardiac catheterization studies indicate that some patients have a decrease in valve area of 0.1 to 0.3 cm^2 per year; the systolic pressure gradient across the valve may increase by as much as 10 to 15 mm Hg per year (72–78). However, more than half of the reported patients show little or no progression over a 3- to 9-year period. Doppler echocardiographic data obtained over several years are consistent with those obtained with cardiac catheterization. Some patients exhibit a significant increase in transvalvular pressure gradient (≈15 to 19 mm Hg per year) and a decrease in valve area; others show little or no change (79–83). The average rate of change is ≈0.12 cm^2 per year (84). 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 (41,73), it is not possible to predict the rate of progression in an individual patient. For this reason, careful clinical follow-up is mandatory in all patients with moderate to severe AS.

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 less than 2 to 3 years (85–90). Thus, the development of symptoms identifies a critical point in the natural history of AS. Management decisions are based largely on these natural history data; many clinicians treat asymptomatic patients conservatively, whereas corrective surgery is generally recommended in patients with symptoms thought to be due to AS.

Sudden death is known to occur in patients with severe AS and rarely has been documented to occur without prior symptoms (85,88,91). These older retrospective studies emphasize the possibility of sudden death in asymptomatic patients. However, prospective echocardiographic studies provide important data on the rarity of sudden death in asymptomatic patients (Table 11). In one report, 51 asymptomatic patients with severe AS were followed for an average of 17 months. In this study, 2 patients died; symptoms preceded death in both cases (90). In another report of 113 patients followed for 20

Table 11. Studies of the Natural History of Asymptomatic Patients With Aortic Stenosis

Study, y	Number of patients	Mean follow-up, year	Severity of aortic stenosis	Sudden death without symptoms (number of patients)	Comments
Chizner et al 1980 (91)	8	5.7	AVA <1.1 cm^2	0	retrospective study
Turina et al 1987 (77)	17	2.0	AVA <0.9 cm^2	0	retrospective study
Horstkotte and Loogen 1988 (88)	35	"years"	AVA = 0.4–0.8 cm^2	3	retrospective study
Kelly et al 1988 (90)	51	1.5	PV = 3.5–5.8 m/s	0	prospective study
Pellikka et al 1990 (92)	113	1.7	PV >4.0 m/s	0	prospective study
Faggiano et al 1992 (81)	37	2.0	AVA = 0.85 ± 0.15 cm^2	0	prospective study
Otto et al 1997 (84)	114	2.5	PV = 3.6 ± 0.6 m/s	0	prospective study
Total	375	2.1		3	average risk of sudden death ≈0.4%/y

Abbreviations: AVA = aortic valve area; PV = peak instantaneous velocity

months, there were no cases of sudden death without preceding symptoms; in this study, survival was no different from that of an age- and sex-matched control group (92). In this latter study, all patients had Doppler velocities across the aortic valve ≥4 m/s. However, only one third had aortic valve velocities ≥5 m/s, and a number of patients were not included in the follow-up analysis because they underwent AVR at the discretion of the clinician. In a third report of 123 patients followed for an average of 30 months, there were no cases of sudden death (84). These findings were similar in 2 smaller studies (77,81). Therefore, although sudden death occasionally does occur in the absence of preceding symptoms in patients with AS (85,88,93), it must be an uncommon event—probably <1% per year.

4. Management of the Asymptomatic Patient. Many asymptomatic patients with severe AS develop symptoms within a few years and require surgery. In one series, the incidence of angina, dyspnea, or syncope in 113 asymptomatic patients with Doppler outflow velocities ≥4 m/s was 14% after 1 year and 38% after 2 years (92). In another report of 123 asymptomatic patients, the rate of symptom development was 38% at 3 years for the total group but 79% at 3 years in patients with Doppler outflow velocity ≥4 m/s (84). Therefore, patients with severe AS require careful monitoring for development of symptoms and progressive disease.

a. Initial Evaluation. The diagnosis of severe AS can usually be made on the basis of the systolic outflow murmur, delayed and diminished carotid upstrokes, sustained LV impulse, and reduced intensity of the aortic component of the second heart sound. Paradoxical splitting of the second sound may be present. In the elderly, the pulsus tardus and parvus may be absent because of the effects of aging on the vasculature. Patients presenting with the physical findings of AS should undergo selected laboratory examinations, including an ECG, a chest x-ray, and an echocardiogram. The 2-D echocardiogram is valuable for confirming the presence of aortic valve disease and determining the LV response to pressure overload. In most patients, the severity of the stenotic lesion can be defined with Doppler echocardiographic measurements of a mean transvalvular pressure gradient and a derived valve area, as discussed in the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2). The mean pressure gradient may be underestimated if the Doppler beam is not parallel to the velocity jet; however, it may occasionally overestimate the transvalvular gradient, especially in the patient with a small aortic root and/or high cardiac output. Thus, the pressure gradient and derived valve area require meticulous attention to measurement of LV outflow tract area and velocity. Echocardiography is also used to assess LV size and function, degree of hypertrophy, and presence of other associated valvular disease.

Recommendations for Echocardiography in Aortic Stenosis

Indication	*Class*
1. Diagnosis and assessment of severity of AS.	**I**
2. Assessment of LV size, function, and/or hemodynamics.	**I**
3. Reevaluation of patients with known AS with changing symptoms or signs.	**I**
4. Assessment of changes in hemodynamic severity and ventricular function in patients with known AS during pregnancy.	**I**
5. Reevaluation of asymptomatic patients with severe AS.	**I**
6. Reevaluation of asymptomatic patients with mild to moderate AS and evidence of LV dysfunction or hypertrophy.	**IIa**
7. Routine reevaluation of asymptomatic adult patients with mild AS having stable physical signs and normal LV size and function.	**III**

From the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2).

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 the patient is symptomatic and AVR is planned.

Exercise testing in adults with AS has been discouraged largely because of concerns about safety. Furthermore, when used to assess the presence or absence of CAD, the test has limited diagnostic accuracy. Presumably, this is due to the presence of an abnormal baseline ECG, LV hypertrophy, and limited coronary flow reserve. Certainly, exercise testing should not be performed in symptomatic patients. However, in asymptomatic patients, exercise testing is safe and may provide information that is not uncovered during the initial clinical

evaluation (94–97). 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. Such testing can identify patients with a limited exercise capacity or even exercise-induced symptoms despite a negative medical history. Although the prognostic significance of electrocardiographic ST depression is unknown, an abnormal hemodynamic response (eg, hypotension) in a patient with severe AS is sufficient reason to consider AVR. Finally, in selected patients, the observations made during exercise may provide a basis for advice about physical activity.

The frequency of follow-up visits to the physician depends on the severity of the valvular stenosis and in part 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 mild AS. Those with moderate and severe AS should be examined more frequently. Patients should be advised to promptly report the development of any exertional chest discomfort, dyspnea, lightheadedness, or syncope.

b. Serial Testing. Echocardiographic studies can be an important part of an integrated approach that includes a detailed history, physical examination, and in some patients a carefully monitored exercise test. Recognizing that the rate of progression varies considerably, clinicians often perform an annual echocardiogram on patients known to have moderate to severe AS. However, current understanding of the natural history of AS and indications for surgical intervention do not support the use of annual echocardiographic studies to assess changes in valve area as such. However, serial echocardiograms are helpful for assessing changes in LV hypertrophy and function. Therefore, in patients with severe AS, an echocardiogram every year may be appropriate. In patients with moderate AS, serial studies performed every 2 years or so are satisfactory, and in patients with mild AS, serial studies can be performed every 5 years. Echocardiograms should be performed more frequently if there is a change in clinical findings. In patients with echocardiograms of suboptimal quality, cardiac magnetic resonance imaging may be used to assess LV volume, wall thickness, mass, and systolic function (98–102) as well as severity of AS (103,104). In centers with specific expertise in cardiac magnetic resonance imaging, serial magnetic resonance imaging may be performed in place of serial echocardiograms.

c. Medical Therapy. Antibiotic prophylaxis is indicated for prevention of infective endocarditis and, in those with rheumatic AS, recurrent episodes of rheumatic fever. 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, and patients who develop symptoms require surgery, not medical therapy. Most asymptomatic patients lead a normal life, although restriction of physical activity should be advised in most patients with moderate or severe AS.

d. 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 26th Bethesda Conference (105). Physical activity is not restricted in asymptomatic patients with mild AS; these patients can participate in competitive sports. Patients with moderate 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. Patients with severe AS should be advised to limit their activity to relatively low levels.

5. Indications for Cardiac Catheterization. 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 detail in section VIII of these guidelines. 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 or there is evidence of associated valvular or congenital disease or pulmonary hypertension.

Recommendations for Cardiac Catheterization in Aortic Stenosis

Indication	*Class*
1. Coronary angiography before AVR in patients at risk for CAD (see section VIII.B. of these guidelines).	**I**
2. Assessment of severity of AS in symptomatic patients when AVR is planned or when noninvasive tests are inconclusive or there is a discrepancy with clinical findings regarding severity of AS or need for surgery.	**I**
3. Assessment of severity of AS before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed.	**IIb**
4. Assessment of LV function and severity of AS in asymptomatic patients when noninvasive tests are adequate.	**III**

The pressure gradient across a stenotic valve is related to the valve orifice area and the transvalvular flow (106). Thus, in the presence of depressed cardiac output, relatively low pressure gradients are frequently obtained in patients with severe AS. On the other hand, during exercise or other high flow states, systolic gradients can be measured in minimally stenotic valves. For these reasons, complete assessment of AS requires (1) measurement of transvalvular flow, (2) determination of the transvalvular pressure gradient, and (3) calculation of the effective valve area. Careful 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.

a. Low-Gradient Aortic Stenosis. Patients with severe AS and low cardiac output often present with only modest transvalvular pressure gradients (ie, <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. The standard valve area formula is less accurate and is known to underestimate the valve area in low-flow states, and under such conditions, it should be interpreted with caution. In theory, Doppler-derived valve areas should be less susceptible to low flow, but this does not appear to be borne out in clinical practice. It has been suggested that valve resistance might provide a better separation between critical and noncritical AS, particularly in patients with low transvalvular pressure gradients (107,108). Although valve resistance is less sensitive to flow than valve area, the resistance calculations have not been proved to be substantially better than valve area calculations.

In patients with low-gradient stenosis and what appears to be moderate to severe AS, it may be useful to determine the transvalvular pressure gradient and to calculate valve area and resistance during a baseline state and again during exercise or pharmacological (ie, dobutamine infusion) stress (97,109–111). This approach is based on the notion that patients who do not have true, anatomically severe stenosis exhibit an increase in the valve area during an increase in cardiac output (109,110). Thus, if a dobutamine infusion produces an increment in stroke volume, an increase in valve area, and a decrease in valve resistance, it is likely that the baseline calculations overestimated the severity of the stenosis. In patients with severe AS, these changes may result in a calculated valve area that is higher than the baseline calculation but one that remains in the severe range, whereas in patients without severe AS, the calculated valve area with dobutamine will fall outside the severe range and indicate that severe AS is not present.

6. Indications for Aortic Valve Replacement. In the vast majority of adults, AVR is the only effective treatment for severe AS. However, younger patients may be candidates for valvotomy (see section VI.A. of these guidelines). Although there is some lack of agreement about the optimal timing of surgery, particularly in asymptomatic patients, it is possible to develop rational guidelines for most patients. Particular consideration should be given to the natural history of symptomatic and asymptomatic patients and to operative risks and outcomes after surgery.

a. Symptomatic Patients. Patients with angina, dyspnea, or syncope exhibit symptomatic improvement and an increase in survival after AVR (86,112–116). These salutary results of surgery are partly dependent on the state of 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 of the patients in this latter group is caused by excessive afterload (afterload mismatch [52]), and LV function improves after AVR in such patients. If LV dysfunction is not caused by afterload mismatch, then improvement in LV function and resolution of symptoms may not be complete after valve replacement (116). Survival is still improved in this setting (112), with the possible exception of patients with severe LV dysfunction caused by CAD (116). Therefore, in the absence of serious comorbid conditions, AVR is indicated in virtually all symptomatic patients with severe AS. However, patients with severe LV dysfunction, particularly those with so-called low gradient AS, create a difficult management decision (117) (see above). AVR should not be performed in such patients if they do not have anatomically severe AS. In patients who do have severe AS, even those with a low transvalvular pressure gradient, AVR results in hemodynamic improvement and better functional status.

b. Asymptomatic Patients. Many clinicians are reluctant to proceed with AVR in an asymptomatic patient (118), whereas others are concerned about following a patient with severe AS. Although insertion of a prosthetic aortic valve is associated with low perioperative morbidity and mortality, long-term morbidity and mortality can be appreciable for mechanical and bioprosthetic valves. Significant complications occur at the rate of at least 2% to 3% per year, and death due directly to the prosthesis occurs at the rate of ≈1% per year (119–124). Thus, even if surgical mortality can be minimized, the combined risk of surgery and the late complications of a prosthesis exceed the possibility of preventing sudden death and prolonging survival in all asymptomatic patients, as discussed previously. Despite these considerations, some difference of opinion persists among clinicians regarding the indications for corrective surgery in asymptomatic patients. Some argue that irreversible myocardial depression and/or fibrosis may develop during a prolonged asymptomatic stage and that this may preclude an optimal outcome. Such irreversibility has not been proved, but this concept has been used to support early surgery (114,125). Still others attempt to identify patients who may be at especially high risk of sudden death without surgery, although data supporting this approach are limited. Patients in this subgroup include those who have an abnormal response to exercise (eg, hypotension), those with LV systolic dysfunction or marked/excessive LV hypertrophy, or those with evidence of very severe AS. However, it should be recognized that such "high-risk" patients are rarely asymptomatic.

c. Patients Undergoing Coronary Artery Bypass Surgery. Patients with severe AS, with or without symptoms, who are undergoing coronary artery bypass surgery should undergo AVR at the time of the revascularization procedure. Similarly, patients with severe AS undergoing surgery on other valves

(such as mitral valve repair) or the aortic root should also undergo AVR as part of the surgical procedure, and it is generally accepted practice to perform AVR in patients with moderate AS (for example, gradient ≥30 mm Hg) who are undergoing mitral valve or aortic root surgery, as discussed in sections III.F.6. and III.F.7. of these guidelines. Such patients with moderate AS may also warrant AVR at the time of coronary artery bypass surgery, but there are limited data to support this policy. Greater controversy persists regarding the indications for concomitant AVR at the time of coronary artery bypass surgery in patients with milder forms of AS, as discussed in section VIII.D. of these guidelines.

Recommendations for Aortic Valve Replacement in Aortic Stenosis

Indication	*Class*
1. Symptomatic patients with severe AS.	I
2. Patients with severe AS undergoing coronary artery bypass surgery.	I
3. Patients with severe AS undergoing surgery on the aorta or other heart valves.	I
4. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves (see sections III.F.6., III.F.7., and VIII.D. of these guidelines).	IIa
5. Asymptomatic patients with severe AS and	
· LV systolic dysfunction	IIa
· Abnormal response to exercise (eg, hypotension)	IIa
· Ventricular tachycardia	IIb
· Marked or excessive LV hypertrophy (≥15 mm)	IIb
· Valve area <0.6 cm^2	IIb
6. Prevention of sudden death in asymptomatic patients with none of the findings listed under indication 5.	III

7. Aortic Balloon Valvotomy. Percutaneous balloon aortic valvotomy is a procedure in which one or more balloons are placed across a stenotic valve and inflated to decrease the severity of stenosis (126–128). This procedure has an important role in treating adolescents and young adults with AS (see section VI.A.) 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 some degree stretching of the annulus and separation of the calcified or fused commissures (129–131). 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 complications occur with a frequency >10% (132–138); restenosis and clinical deterioration occur within 6 to 12 months in most patients (133,138–141). Therefore, in adults with AS, balloon valvotomy is not a substitute for AVR (141–144).

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 (144). For example, patients with severe AS and refractory pulmonary edema or cardiogenic shock may benefit from aortic valvuloplasty as a "bridge" to surgery; an improved hemodynamic state may reduce the risks of surgery. The indications for palliative valvotomy in patients with serious comorbid conditions are less well established, but most patients can expect temporary relief of symptoms despite a very limited life expectancy. Asymptomatic patients with severe AS who require urgent noncardiac surgery may be candidates for valvotomy, but most such patients can be successfully treated with more conservative measures (145,146).

Recommendations for Aortic Balloon Valvotomy in Adults With Aortic Stenosis*

Indication	*Class*
1. A "bridge" to surgery in hemodynamically unstable patients who are at high risk for AVR.	IIa
2. Palliation in patients with serious comorbid conditions.	IIb
3. Patients who require urgent noncardiac surgery.	IIb
4. An alternative to AVR.	III

*Recommendations for aortic balloon valvotomy in adolescents and young adults with AS are provided in section VI.A. of these guidelines.

8. Medical Therapy for the Inoperable Patient. Comorbid conditions (eg, malignancy) or, on occasion, patient preferences may preclude corrective surgery. Under such circumstances, limited medical therapies are available to control symptoms. Patients with evidence of pulmonary congestion can benefit from 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. 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 with digitalis or perhaps amiodarone is essential. Efforts should be made to prevent atrial fibrillation, especially development of a rapid ventricular response. β-Adrenergic receptor blocking agents as well as other drugs with negative inotropic effects should not be used in patients with heart failure caused by AS. If angina is the predominant symptom, cautious use of nitrates and β-blockers can provide relief. There is no specific medical therapy for syncope unless it is caused by a bradyarrhythmia or tachyarrhythmia.

9. Evaluation After Aortic Valve Replacement. AVR should be considered a form of palliative therapy in that a prosthetic valve with its attendant complications is substituted for a diseased native valve (119–124). Patients with prosthetic heart valves therefore require periodic clinical and selected laboratory examinations. A complete history and physical examination should be performed at least once a year. Indications for echocardiography are discussed in section VII.C.3. of these guidelines.

10. 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 (147), 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 coronary disease or ventricular dysfunction (87). Certainly advanced cancer and permanent neurological defects as a result of stroke make cardiac surgery inappropriate. Deconditioned and debilitated patients often do not return to an active existence, and the presence of the other comorbid disorders may 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 may 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 (66,68). Preoperative recognition of elderly patients with marked LV hypertrophy followed by appropriate perioperative management may substantially reduce this morbidity and mortality. There is no perfect method for weighing all of the relevant factors and identifying specifically high- and low-risk elderly patients (148). The decision to proceed with valve replacement depends on an imprecise analysis that considers the balance between the potential for improved symptoms and survival and the morbidity and mortality of surgery.

B. Aortic Regurgitation

1. Etiology. There are a number of common causes of AR. These include idiopathic dilatation, congenital abnormalities of the aortic valve (most notably bicuspid valves), calcific degeneration, rheumatic disease, infective endocarditis, systemic hypertension, myxomatous proliferation, dissection of the ascending aorta, and Marfan syndrome. Less common etiologies 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 III.H. of these guidelines). The majority of these lesions produce chronic AR with slow, insidious LV dilatation and a prolonged asymptomatic phase. 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.

2. Acute Aortic Regurgitation

a. 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 and/or cardiogenic shock. Acute AR creates especially marked hemodynamic changes in patients with preexisting 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 preexisting AS, and acute regurgitation after balloon valvotomy or surgical commissurotomy for congenital AS.

b. Diagnosis. Many of the characteristic physical findings of chronic AR are modified or absent when valvular regurgitation is acute, which may 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 may occur before the end of diastole, the diastolic murmur may be short and/or soft and therefore poorly heard. The elevated LV diastolic pressure may close the mitral valve prematurely, reducing the intensity of the first heart sound. An apical diastolic rumble may 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, in determining its etiology, in estimating the degree of pulmonary hypertension (if TR is present), and in determining whether there is rapid equilibration of aortic and LV diastolic pressure. Evidence for rapid pressure equilibration includes a short AR diastolic half-time (<300 ms), a short mitral deceleration time (<150 ms), or premature closure of the mitral valve.

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 (149–151). If the diagnosis remains uncertain, cardiac catheterization and aortography should be performed. Coronary angiography is an important component of the evaluation of aortic dissection and acute AR and should be performed, provided that it does not delay

urgent surgery. In some patients, other diagnostic imaging methods, such as computed tomographic imaging or magnetic resonance imaging, may be required if echocardiography does not provide the diagnosis and angiography is not planned (149,150,152).

c. Treatment. Death from pulmonary edema, ventricular arrhythmias, electromechanical dissociation, or circulatory collapse is common in acute severe AR, even with intensive medical management. Early 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 operation. Intra-aortic balloon counterpulsation is contraindicated. Although β-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 IV.E. of these guidelines.

3. Chronic Aortic Regurgitation

a. 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 (153). 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 (154). 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 concentric hypertrophy (153,155). Thus, AR represents a condition of combined volume overload and pressure overload (156). As the disease progresses, recruitment of preload reserve and compensatory hypertrophy permit the ventricle to maintain normal ejection performance despite the elevated afterload (157,158). 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 overall LV function is usually not "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 (158) and/or the hypertrophic response may be inadequate (48), 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 develop dyspnea at this point in the natural history, which is related to declining systolic function or elevated filling pressures. In addition, diminished coronary flow reserve in the hypertrophied myocardium may result in exertional angina (159). 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 (160–171). 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 (169,172–181).

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 (160–170,172–189). Studies of predictors of surgical outcome are listed in Table 12.

Among patients undergoing valve replacement for chronic AR with preoperative LV systolic dysfunction (defined as an ejection fraction below normal at rest), several factors are associated with worse functional and survival results after operation. These are listed in Table 13.

b. Natural History. (1) ASYMPTOMATIC PATIENTS WITH NORMAL LV 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 7 published series (190–197) involving a total of 490 such patients (range, 27 to 104 patients/series) with a mean follow-up period of 6.4 years (Table 14). This analysis is subject to the usual limitations of comparing different clinical

Table 12. Preoperative Predictors of Surgical Outcome in Aortic Regurgitation

Study, year	Study design	Number of patients	Outcome assessed	Findings
Forman et al 1980 (175)	Retrospective	90	Survival	High-risk group identified by preoperative angiographic LV EF <0.50.
Henry et al 1980 (182)	Prospective	50	Survival	High-risk group identified by preoperative echocardiographic LV FS <0.25 and/or ESD >55 mm.
Cunha et al 1980 (176)	Retrospective	86	Survival	High-risk group identified by preoperative echocardiographic LV FS <0.30. Mortality also significantly associated with preoperative ESD. Among patients with FS <0.30, mortality higher in NYHA FC III–IV than in FC I–II.
Greves et al 1981 (177)	Retrospective	45	Survival	High-risk group identified by preoperative angiographic LV EF <0.45 and/or CI <2.5 L/min. Among patients with EF <0.45, mortality higher in NYHA FC III–IV than in FC I–II.
Kumpuris et al 1982 (183)	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 (178)	Prospective	32	Symptoms, LV function	Persistent LV dilatation after AVR predicted by echocardiographic LV ESD >2.6 cm/m^2, EDD >3.8 cm/m^2 and radius/thickness ratio >3.8. Trend toward worse survival in patients with persistent LV dilatation.
Fioretti et al 1983 (184)	Retrospective	47	LV function	Persistent LV dysfunction predicted by preoperative EDD ≥75 mm and/or ESD ≥55 mm.
Stone et al 1984 (185)	Prospective	113	LV function	Normal LV function after AVR predicted by preoperative LV FS >0.26, ESD <55 mm, and EDD <80 mm. No preoperative variable predicted postoperative LV function.
Bonow et al 1985, 1988 (179, 170)	Prospective	80	Survival, LV function	Postoperative survival and LV function predicted by preoperative LV EF, FS, 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 (186)	Retrospective	84	Survival, symptoms, LV function	Outcome after AVR predicted by preoperative LV FS and ESD. Survival at 2.5 y was 90.5% with FS >0.25 and ESD ≤55 mm but only 70% with ESD >55 mm and FS ≤25%.
Cormier et al 1986 (187)	Prospective	73	Survival	High-risk group identified by preoperative LV EF <0.40 and ESD ≥55 mm.
Sheiban et al 1986 (188)	Retrospective	84	Survival	High-risk group identified by preoperative LV EF <0.50 and ESD >55 mm.
Carabello et al 1987 (168)	Retrospective	14	LV function	Postoperative LV EF predicted by preoperative ESD, FS, EDD, radius/thickness ratio.
Taniguchi et al 1987 (169)	Retrospective	62	Survival	High-risk group identified by preoperative ESV >200 mL/m^2 and/or EF <0.40.
Michel et al 1995 (181)	Retrospective	286	LV function	Postoperative LV dysfunction predicted by preoperative LV EF, FS, ESD, EDD.
Klodas et al 1996 (189)	Retrospective	219	Survival	High-risk group identified by preoperative EF <0.50.

Abbreviations: 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.

series with different patient selection factors and different end points. For example, 1 series (192) represents patients receiving placebo in a randomized drug trial (198) that included some patients with "early" New York Heart Association (NYHA) functional Class II symptoms (although none had "limiting" symptoms), and another (196) represents patients receiving digoxin in a long-term study comparing the effects of nifedipine with digoxin. In another study (197), 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%).

Table 13. 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 LV ejection fraction
Duration of preoperative LV systolic dysfunction

The results of these 7 studies are summarized in Tables 14 and 15. The rate of progression to symptoms and/or LV systolic dysfunction averaged 4.3% per year. Sudden death occurred in 6 of the 490 patients, an average mortality rate of <0.2% per year. Six of the 7 studies reported the rate of development of asymptomatic LV dysfunction (191–194,196,197); 36 of a total of 463 patients developed depressed systolic function at rest without symptoms during a mean 5.9-year follow-up period, a rate of 1.3% 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 (191–194,196). Thus, careful questioning of patients regarding symptomatic status is not sufficient in the serial evaluation of

Table 14. Studies of the Natural History of Asymptomatic Patients With Aortic Regurgitation

Study, year	Number of patients	Mean follow-up, y	Progression to symptoms, death, or LV dysfunction, rate/y	Progression to asymptomatic LV dysfunction		Mortality (no. of patients)	Comments
				(n)	(rate/y)		
Bonow et al 1983, 1991 (190, 193)	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 (191)*	30	4.7	2.1%	3	2.1%	0	3 patients developing asymptomatic LV dysfunction initially had lower PAP/ESV ratios and trend toward higher LV ESD and EDD and lower FS
Siemienczuk et al 1989 (192)	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
Tornos et al 1995 (194)	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 (195)	27	14.2	3.6%	—	—	0	Development of symptoms predicted by systolic BP, LV ESD, EDD, mass index, and wall thickness
Scognamiglio et al 1994 (196)*	74	6.0	5.7%	15	3.4%	0	All patients received digoxin in a randomized drug trial
Borer et al 1998 (197)	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
Average	490	6.4	4.3%	36	1.3%	(0.19%/y)	
Average in asymptomatic series	336	6.5	3.7%	28	1.6%	(0.09%/y)	Excludes series of Borer et al and Siemienczuk et al

Abbreviations: BP = 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, PAP = pulmonary artery pressure. *Two studies by same authors involved separate patient groups.

asymptomatic patients, and 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. Three of the natural history studies provide concordant information on the variables associated with higher risk (192–194). These are age, LV end-systolic dimension (or volume), and LV end-diastolic dimension (or volume). The LV ejection fraction during exercise, which is also identified in these studies, may not be an independent risk factor as the direction and magnitude of change in ejection fraction from rest to exercise is related not only to myocardial contractility (199) but also severity of volume overload (193,200–202) and exercise-induced changes in preload and peripheral resistance (203). In a multivariate analysis (193), 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. During a mean follow-up period of 8 years, patients with initial end-systolic dimensions >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 <40 mm, it was zero (193).

Table 15. Natural History of Aortic Regurgitation

Asymptomatic patients with normal LV systolic function (190–197):	
· Progression to symptoms and/or LV dysfunction	<6%/y
· Progression to asymptomatic LV dysfunction	<3.5%/y
· Sudden death	<0.2%/y
Asymptomatic patients with LV systolic dysfunction (204–206):	
· Progression to cardiac symptoms	>25%/y
Symptomatic patients (207–209):	
· Mortality rate	>10%/y

(2) ASYMPTOMATIC PATIENTS WITH DEPRESSED SYSTOLIC FUNCTION. The limited data in asymptomatic patients with depressed LV ejection fraction indicate that the majority develop symptoms warranting operation within 2 to 3 years (204–206). The average rate of symptom onset in such patients is >25% per year (Table 15).

(3) SYMPTOMATIC PATIENTS. There are no recent 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 >10% per year have been reported in patients with angina pectoris and >20% per year in those with heart failure (207–209). 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, more recent data indicate a poor outcome of symptomatic patients with medical therapy, even among those with preserved LV systolic function (195,210).

c. Diagnosis and Initial Evaluation of the Asymptomatic Patient. The diagnosis of chronic severe AR can usually be made on the basis of the diastolic murmur, displaced LV impulse, wide pulse pressure, and the characteristic peripheral findings reflecting 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 (211,212). In many patients with more mild to moderate AR, the physical examination will identify the regurgitant lesion but will be less 2accurate in determining its severity. When the diastolic murmur of AR is louder in the third and fourth right intercostal spaces compared with the third and fourth left intercostal spaces, the AR likely results from aortic root dilatation rather than from a deformity of the leaflets alone (213). 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; assess the cause of AR as well as valve morphology; provide a semiquantitative estimate of the severity of regurgitation; assess LV dimension, mass, and systolic function; and 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. Quantitative measurements of LV cavity size and systolic function from 2-D–guided M-mode tracings are more reproducible than and hence preferable to quantitative measurements made directly from 2-D images. In addition to semiquantitative assessment of the severity of regurgitation by color flow jet area and width by Doppler echocardiography, indirect measures of severity of regurgitation 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 (2,214,215). Comparison of stroke volumes at the aortic valve compared with another uninvolved valve may provide a quantitative measurement of regurgitant fraction (216), but this measurement should be made only in experienced laboratories.

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 (with the semiquantitative methods noted above) in addition to LV cavity dilatation.

Recommendations for Echocardiography in Aortic Regurgitation

Indication	*Class*
1. Confirm presence and severity of acute AR.	**I**
2. Diagnosis of chronic AR in patients with equivocal physical findings.	**I**
3. Assessment of etiology of regurgitation (including valve morphology and aortic root size and morphology).	**I**
4. Assessment of LV hypertrophy, dimension (or volume), and systolic function.	**I**
5. Semiquantitative estimate of severity of AR.	**I**
6. Reevaluation of patients with mild, moderate, or severe regurgitation with new or changing symptoms.	**I**
7. Reevaluation of LV size and function in asymptomatic patients with severe regurgitation (recommended timing of reevaluation is given in Figure 2).	**I**
8. Reevaluation of asymptomatic patients with mild, moderate, or severe regurgitation and enlarged aortic root.	**I**
9. Yearly reevaluation of asymptomatic patients with mild to moderate regurgitation with stable physical signs and normal or near-normal LV chamber size.	**III**

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 (Figure 2). If the echocardiogram is of insufficient quality to assess LV function, radionuclide angiography 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 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 (190,192–194,197,200–202,206,217–222). 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 (197) 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 mm 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 demonstrated.

Recommendations for Exercise Testing in Chronic Aortic Regurgitation*

Indication	*Class*
1. Assessment of functional capacity and symptomatic responses in patients with a history of equivocal symptoms.	I
2. Evaluation of symptoms and functional capacity before participation in athletic activities.	IIa
3. Prognostic assessment before AVR in patients with LV dysfunction.	IIa
4. Exercise hemodynamic measurements to determine the effect of AR on LV function.	IIb
5. Exercise radionuclide angiography for assessing LV function in asymptomatic or symptomatic patients.	IIb
6. Exercise echocardiography or dobutamine stress echocardiography for assessing LV function in asymptomatic or symptomatic patients.	III

*These recommendations differ from the ACC/AHA Guidelines for Exercise Testing (3). The committee believes that indications 1, 2, and 3 above warrant a higher recommendation than IIb.

Recommendations for Radionuclide Angiography in Aortic Regurgitation

Indication	*Class*
1. Initial and serial assessment of LV volume and function at rest in patients with suboptimal echocardiograms or equivocal echocardiographic data.*	I
2. Serial assessment of LV volume and function at rest when serial echocardiograms are not used.*	I
3. Assessment of LV volume and function in asymptomatic patients with moderate to severe regurgitation when echocardiographic evidence of declining LV function is suggestive but not definitive.*	I
4. Confirmation of subnormal LV ejection fraction before recommending surgery in an asymptomatic patient with borderline echocardiographic evidence of LV dysfunction.*	I
5. Assessment of LV volume and function in patients with moderate to severe regurgitation when clinical assessment and echocardiographic data are discordant.*	I
6. Routine assessment of exercise ejection fraction.	IIb
7. Quantification of AR in patients with unsatisfactory echocardiograms.	IIb
8. Quantification of AR in patients with satisfactory echocardiograms.	III
9. Initial and serial assessment of LV volume and function at rest in addition to echocardiography.	III

*In centers with expertise in cardiac magnetic resonance imaging (MRI), cardiac MRI may be used in place of radionuclide angiography for these indications.

d. Medical Therapy. 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, or nifedipine reduces peripheral vascular resistance and results in an immediate augmentation in forward cardiac output and a decrease in regurgitant volume (223–231). With nitroprusside and hydralazine, these acute hemodynamic changes lead to a consistent reduction in end-diastolic volume and an increase in ejection fraction (223–226). This is an inconsistent finding with a single oral dose of nifedipine (228–231). 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 (198,232); with nifedipine, these effects are associated with a reduction in LV mass (196,232). Less consistent results have been reported with ACE inhibitors, depending on the degree of reduction in arterial pressure and end-diastolic volume (233–235). Reduced blood pressure with enalapril and quinapril has been associated with decreases in end-diastolic volume and mass but no change in ejection fraction (234,235).

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.

Only 1 study, which compared long-acting nifedipine with digoxin therapy in a total of 143 patients followed for 6 years, has evaluated whether vasodilating therapy alters the long-term natural history of chronic asymptomatic AR in a favorable manner (196). Patients receiving nifedipine had a more gradual rate of attrition due to onset of symptoms and/or LV dysfunction; long-acting nifedipine reduced the need for valve replacement over 6 years from 34% to 15%. Moreover, when patients receiving nifedipine did undergo AVR because of symptoms or impaired systolic function, all survived surgery, and LV size and function improved considerably in all patients (196). Thus, nifedipine does not appear to obscure the development of important signs and symptoms that precede the development of irreversible LV dysfunction. Whether ACE inhibitors would provide similar long-term results is unclear because plasma renin and peripheral ACE activity may not be increased in asymptom-

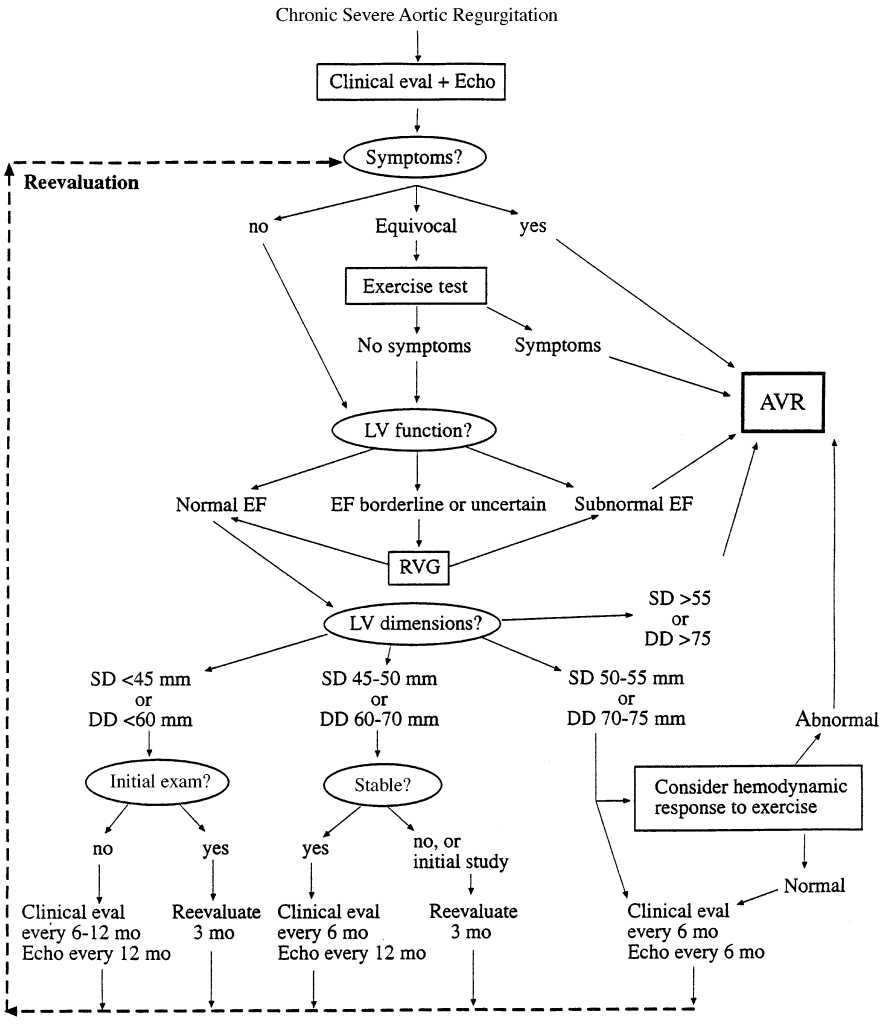

Figure 2. Management strategy for patients with chronic severe aortic regurgitation. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. In some centers, serial follow-up may be performed with RVG or MRI rather than echocardiography to assess LV volume and systolic function. Abbreviations: DD = end-diastolic dimension, RVG = radionuclide ventriculography, SD = end-systolic dimension.

atic patients with uncomplicated chronic AR with normal LV function.

The goal of vasodilator therapy 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 and/or normal LV cavity size.

Vasodilator therapy is not recommended for asymptomatic patients with mild AR and normal LV function in the absence of systemic hypertension, as 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.

Recommendations for Vasodilator Therapy for Chronic Aortic Regurgitation

Indication	*Class*
1. Chronic therapy in patients with severe regurgitation who have symptoms and/or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors.	**I**
2. Long-term therapy in asymptomatic patients with severe regurgitation who have LV dilatation but normal systolic function.	**I**
3. Long-term therapy in asymptomatic patients with hypertension and any degree of regurgitation.	**I**
4. Long-term ACE inhibitor therapy in patients with persistent LV systolic dysfunction after AVR.	**I**
5. Short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction before proceeding with AVR.	**I**
6. Long-term therapy in asymptomatic patients with mild to moderate AR and normal LV systolic function.	**III**

7. Long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for valve replacement.	**III**
8. Long-term therapy in symptomatic patients with either normal LV function or mild to moderate LV systolic dysfunction who are otherwise candidates for valve replacement.	**III**

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.

e. Physical Activity and Exercise. There are no data suggesting that exercise, in particular 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 26th Bethesda Conference (105). 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.

f. 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 reevaluation 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 (Figure 2). 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 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 >60 mm) require more frequent and careful reevaluation, 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 stable, echocardiographic measurements are not required more frequently than every 12 months. In patients with more advanced LV dilatation (end-diastolic dimension >70 mm or end-systolic dimension >50 mm), for whom the risk of developing symptoms or LV dysfunction ranges between 10% and 20% per year (193,194), 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 involving 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 III.B.4. of these guidelines.

Repeat echocardiograms are also recommended when the patient has onset of symptoms, there is an equivocal history of changing symptoms or exercise tolerance, or there are clinical findings suggesting 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 (193) 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 (98–102), cardiac magnetic resonance imaging may also be used to quantify the severity of valvular regurgitation (236–240).

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.

g. Indications for Cardiac Catheterization. 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 VIII of these guidelines. In some patients undergoing left-heart catheterization for coronary angiography, additional aortic root angiography and hemodynamic measurements may provide useful supplementary data.

Recommendations for Cardiac Catheterization in Chronic Aortic Regurgitation

Indication	*Class*
1. Coronary angiography before AVR in patients at risk for CAD (see section VIII.B. of these guidelines).	**I**
2. Assessing severity of regurgitation when noninvasive tests are inconclusive or discordant with clinical findings regarding severity of regurgitation or need for surgery.	**I**
3. Assessing LV function when noninvasive tests are inconclusive or discordant with clinical findings regarding LV dysfunction and need for surgery in patients with severe AR.	**I**
4. Assessment of LV function and severity of regurgitation before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed.	**IIb**
5. Assessment of LV function and severity of regurgitation in asymptomatic patients when noninvasive tests are adequate.	**III**

Hemodynamic and angiographic assessment of 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, other asymptomatic patient subgroups may also require invasive measurement of hemodynamics and/or determination of severity of AR for occupational purposes or for providing recommendations for physical activity and exercise 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 operation (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.

h. Indications for Aortic Valve Replacement. In patients with pure, chronic AR, AVR should be considered only if AR is severe. Patients with only mild AR are not candidates for valve replacement, and if such patients have symptoms or LV dysfunction, other etiologies 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.

(1) SYMPTOMATIC PATIENTS WITH NORMAL LV SYSTOLIC FUNCTION. AVR is indicated in patients with normal systolic function (defined as ejection fraction $\geq$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 etiology 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 etiology 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 operation in a patient who is nearing these values.

(2) SYMPTOMATIC PATIENTS WITH LV DYSFUNCTION. Patients with NYHA functional Class II, III, or IV symptoms and with mild to moderate LV systolic dysfunction (ejection fraction 0.25 to 0.49) should undergo AVR. Patients with functional Class IV symptoms have worse postoperative survival rates and lower likelihood of recovery of systolic function compared with patients with less severe symptoms (170,176,177,179), but AVR will improve ventricular loading conditions and expedite subsequent management of LV dysfunction (163).

Symptomatic patients with advanced LV dysfunction (ejection fraction $<$0.25 and/or end-systolic dimension $>$60 mm) present difficult management issues. Some patients will manifest meaningful recovery of LV function after operation, 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 (1) symptoms and evidence of LV dysfunction are of recent onset and (2) intensive short-term therapy with vasodilators, diuretics, and/or intravenous positive inotropic agents results in substantial improvement in hemodynamics or systolic function. However, even in patients with NYHA functional Class IV symptoms and ejection fraction $<$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 (241).

(3) ASYMPTOMATIC PATIENTS. AVR in asymptomatic patients remains a controversial topic, but it is generally agreed (158,242–246) that valve replacement 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, realizing that this lower limit is technique dependent and may vary among institutions. The committee also realizes that there may be variability in any given measured LV dimension or ejection fraction. Therefore, the committee recommends that 2 consecutive measurements be obtained before proceeding 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 (for example, a second echocardiogram after an initial echocardiogram) or with a separate independent test (for example, a radionuclide ventriculogram or a contrast left ventriculogram after an initial echocardiogram).

Valve replacement is also recommended in patients with severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >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 systolic function despite severe increases in end-systolic and end-diastolic chamber size should be considered for surgery, as they appear to represent a high risk group with an increased incidence of sudden death (193,247), and the results of valve replacement in such patients have thus far been excellent (189). In contrast, postoperative mortality is considerable once patients with severe LV dilatation develop symptoms and/or LV systolic dysfunction (189). The data regarding the risk of sudden death and postoperative outcome with severe LV dilatation have been developed with an LV end-diastolic dimension ≥80 mm, but the committee recommends surgery before the left ventricle achieves this degree of dilatation and recommends AVR for patients with LV end-diastolic dimension >75 mm.

Patients with severe AR in whom the degree of dilatation has not reached but is approaching these threshold values (for example, LV end-diastolic dimension of 70 to 75 mm or end-systolic dimension of 50 to 55 mm) should be followed carefully with frequent echocardiograms every 4 to 6 months, as noted previously (Figure 2). In addition, it is reasonable to recommend AVR 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 ≥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 ventricular dysfunction; and patients with concomitant MS, in whom the left ventricle will not dilate to the same extent as in patients with pure AR (248). In such patients, it is particularly important that systolic function and not merely systolic dimension be monitored. Women also tend to develop symptoms and/or LV dysfunction with less LV dilatation than men (249); this appears to be related to body size as 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 mm 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 an indication for AVR in asymptomatic patients with normal systolic function at rest, because the exercise ejection fraction response is multifactorial and the strength of evidence is limited. The ejection fraction response to exercise has not proved to have independent prognostic value in patients undergoing surgery (179). The change in ejection fraction with exercise is a relatively nonspecific response related to both severity of volume load (193,200–202) and exercise-induced changes in preload and peripheral resistance (203) that develop early in the natural history of AR. Valve replacement 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 <75 mm or end-systolic dimension <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 (193), but such patients often reach a new steady state and may do well for extended periods of time. Hence, valve replacement is not recommended until the threshold values noted above are reached or symptoms or LV systolic dysfunction develop.

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 operation may be reduced. Until such data are available, the indications for operation for AR should not vary with the operative technique to be used.

Recommendations for Aortic Valve Replacement in Chronic Severe Aortic Regurgitation

Indication	*Class*
1. Patients with NYHA functional Class III or IV symptoms and preserved LV systolic function, defined as normal ejection fraction at rest (ejection fraction ≥0.50).	I
2. Patients with NYHA functional class II symptoms and preserved LV systolic function (ejection fraction ≥0.50 at rest) but with progressive LV dilatation or declining ejection fraction at rest on serial studies or declining effort tolerance on exercise testing.	I
3. Patients with Canadian Heart Association functional Class II or greater angina with or without CAD.	I
4. Asymptomatic or symptomatic patients with mild to moderate LV dysfunction at rest (ejection fraction 0.25 to 0.49).	I
5. Patients undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves.	I
6. Patients with NYHA functional Class II symptoms and preserved LV systolic function (ejection fraction ≥0.50 at rest) with stable LV size and systolic function on serial studies and stable exercise tolerance.	IIa
7. Asymptomatic patients with normal LV systolic function (ejection fraction >0.50) but with severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm).*	IIa
8. Patients with severe LV dysfunction (ejection fraction <0.25).	IIb
9. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) and progressive LV dilatation when the degree of dilatation is moderately severe (end-diastolic dimension 70 to 75 mm, end-systolic dimension 50 to 55 mm).	IIb
10. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) but with decline in ejection fraction during	
· Exercise radionuclide angiography	IIb
· Stress echocardiography	III
11. Asymptomatic patients with normal systolic function at rest (ejection fraction >0.50) and LV dilatation when degree of dilatation is not severe (end-diastolic dimension <70 mm, end-systolic dimension <50 mm).	III

*Consider lower threshold values for patients of small stature of either gender. Clinical judgment is required.

4. Concomitant Aortic Root Disease. In addition to causing acute AR, diseases of the proximal aorta may also contribute to chronic AR. 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 caused by hypertension. In such patients, if the AR is mild and/or the left ventricle is only mildly dilated, management should focus on treating the underlying aortic root disease, which is beyond the scope of these guidelines. In many patients, however, AR may be severe and associated with severe LV dilatation and/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 proximal aorta and AR of any severity when the degree of aortic root dilatation reaches or exceeds 50 mm by echocardiography (250).

5. Evaluation of Patients After Aortic Valve Replacement. After AVR, careful follow-up is necessary during the early and long-term postoperative course to evaluate prosthetic valve function and assess LV function, as discussed in detail in section VII.C.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 reevaluation. 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 (251), even though ejection fraction may increase over the subsequent several months. Thus, persistent or more severe systolic dysfunction early after operation 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 two of operation (165,170,252). 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 (165,170,252), and the magnitude of reduction in end-diastolic dimension after surgery correlates with the magnitude of increase in ejection fraction (170).

After the initial postoperative reevaluation, the patient should be seen and examined again at 6 months and 12 months and then on a yearly basis if the clinical course is uncomplicated. If the patient is asymptomatic and 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 any other patient with symptomatic or asymptomatic LV dysfunction, including treatment with ACE inhibitors. In such patients, repeat echocardiography to assess LV size and systolic function is warranted at the 6- and 12-month reevaluations. 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 VII.C.3. of these guidelines.

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 (253). Elderly patients with AR generally fare less well than patients in young or middle age. Patients older than 75 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 postop-

erative 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.

C. Mitral Stenosis

1. Pathophysiology and Natural History. MS is an obstruction to LV inflow at the level of the mitral valve as a result of a structural abnormality of the mitral valve apparatus, preventing 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 ≈60% of patients presenting with pure MS (254,255). The ratio of women to men presenting with isolated MS is 2:1 (254–256). Congenital malformation of the mitral valve occurs rarely and is observed mainly in infants and children (257).

In patients with MS from rheumatic fever, the pathological process causes leaflet thickening and calcification, commissural fusion, chordal fusion, or a combination of these processes (257,258). 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 (257,258).

The normal mitral valve area is 4.0 to 5.0 cm^2. Narrowing of the valve area to <2.5 cm^2 must occur before the development of symptoms (106). 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 (259) and results in elevation of left atrial pressure, which is reflected back into the pulmonary venous circulation. 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. The pulmonary arterioles react with vasoconstriction, intimal hyperplasia, and medial hypertrophy, which lead to pulmonary arterial hypertension.

A mitral valve area >1.5 cm^2 usually does not produce symptoms at rest (260). 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 dependent on the diastolic filling period (106). 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 (260). As the obstruction across the mitral valve increases, there will be increasing symptoms of dyspnea as the left atrial and pulmonary venous pressures increase.

Several other factors influence symptoms in patients with MS. As the severity of stenosis increases, cardiac output becomes subnormal at rest (260) and fails to increase during exercise (261). The degree of pulmonary vascular disease is also an important determinant of symptoms in patients with MS (260,262,263). A second obstruction to flow develops from increased pulmonary arteriolar resistance (262,263), which may protect the lungs from pulmonary edema (262,263). In some patients, an additional reversible obstruction develops at the level of the pulmonary veins (264,265). The low cardiac output and increased pulmonary arteriolar resistance, combined with adaptation of the lungs (alveolar basement membrane thickening, adaptation of neuroreceptors, and increased lymphatic drainage), contribute to the ability of a patient with severe MS to remain minimally symptomatic for prolonged periods of time (260,262,263).

The natural history of patients with untreated MS has been defined from studies in the 1950s and 1960s (254–256). MS 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 (254–256,266). 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 (254). Overall, the 10-year survival of untreated patients presenting with MS is 50% to 60%, depending on symptoms at presentation (255,256). In the asymptomatic or minimally symptomatic patient, survival is >80% at 10 years, with 60% of patients having no progression of symptoms (255,256,266). However, once significant limiting symptoms occur, there is a dismal 0 to 15% 10-year survival (254–256,266,267). Once there is severe pulmonary hypertension, mean survival drops to <3 years (268). The mortality of untreated patients with MS is due to progressive heart failure in 60% to 70%, systemic embolism in 20% to 30%, pulmonary embolism in 10%, and infection in 1% to 5% (256,257). In North America and Europe, this classic history of MS has been replaced by an even milder delayed course with the decline in incidence of rheumatic fever (266,269). The mean age of presentation is now in the fifth to sixth decade (266,269); more than one third of patients undergoing valvotomy are older than 65 years (270). 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 twenties (266).

2. Evaluation and Management of the Asymptomatic Patient. *a. Initial Workup.* The diagnosis of MS should be made on the basis of the history, physical examination, chest x-ray, and ECG (Figure 3). Patients may present with no symptoms but have an abnormal physical examination (266,269). Although some patients may present with fatigue, dyspnea, or

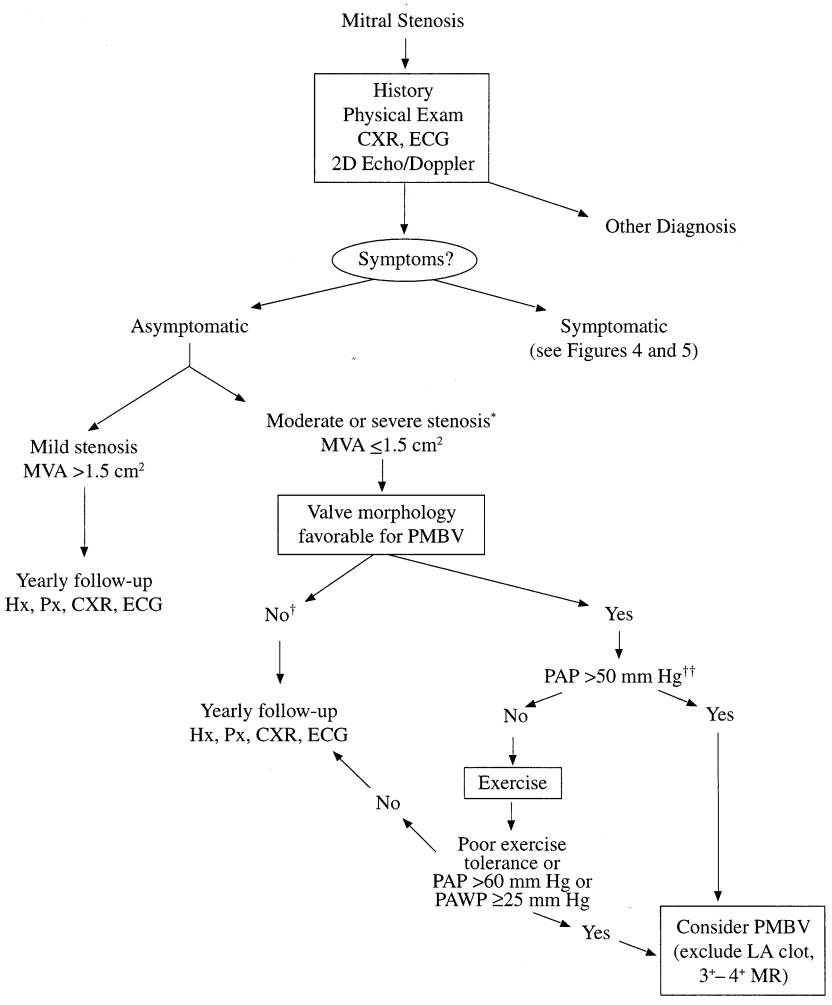

Figure 3. Management strategy for patients with mitral stenosis. Abbreviations: CXR = chest x-ray, LA = left atrial, MVA = mitral valve area, PMBV = percutaneous mitral balloon valvotomy, PAP = pulmonary artery pressure, PAWP = pulmonary artery wedge pressure. *The committee recognizes that there may be variability in the measurement of MVA and that the mean transmitral gradient, PAWP, and PAP should also be taken into consideration. †There is controversy as to whether patients with severe MS (MVA <1.0 cm^2) and severe pulmonary hypertension (PAP >60–80 mm Hg) should undergo MVR to prevent right ventricular failure. ††Assuming no other cause for pulmonary hypertension is present.

frank pulmonary edema, in others, the initial manifestation of MS is the onset of atrial fibrillation or an embolic event (254).

The diagnostic tool of choice in the evaluation of a patient with MS is 2-D and Doppler echocardiography (271–276). Echocardiography is able to identify restricted diastolic opening of the mitral valve leaflets due to "doming" of the anterior leaflet and immobility of the posterior leaflet (271–274). Other entities that can simulate the clinical features of rheumatic MS, such as left atrial myxoma, cor triatriatum, and a parachute mitral valve can be readily identified by 2-D echocardiography. Planimetry of the orifice area may be possible from the short-axis view. 2-D echocardiography can be used to assess the morphological appearance of the mitral valve apparatus, including leaflet mobility, leaflet thickness, leaflet calcification, subvalvular fusion, and the appearance of commissures (277–280). These features may be important when considering the timing and type of intervention to be performed (277–280). Patients with mobile noncalcified leaflets, no commissural calcification, and little subvalvular fusion may be candidates for either balloon catheter or surgical commissurotomy/valvotomy (277–280). Chamber size and function as well as other structural valvular, myocardial, or pericardial abnormalities can be assessed with the 2-D echocardiographic study.

Doppler echocardiography can be used to assess the hemodynamic severity of the obstruction (275,276,281). The mean transmitral gradient can be accurately and reproducibly measured from the continuous wave Doppler signal across the mitral valve with the modified Bernoulli equation (275,276). The mitral valve area can be noninvasively derived from Doppler echocardiography with either the diastolic half-time method (281–284) or the continuity equation (282). The half-time may be inaccurate in patients with abnormalities of left atrial or LV compliance, those with associated AR, and those who have had mitral valvotomy (283,284). Doppler echocardiography should also be used to estimate pulmonary artery systolic pressure from the TR velocity signal (285) 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 (286–289). This allows measurement of both the transmitral gradient (286–288) and pulmonary artery systolic pressure (288,289) at rest and with exercise. Dobutamine stress with Doppler recordings may also be performed (290).

Recommendations for Echocardiography in Mitral Stenosis

Indication	*Class*
1. Diagnosis of MS, assessment of hemodynamic severity (mean gradient, mitral valve area, pulmonary artery pressure), and assessment of right ventricular size and function.	I
2. Assessment of valve morphology to determine suitability for percutaneous mitral balloon valvotomy.	I
3. Diagnosis and assessment of concomitant valvular lesions.	I
4. Reevaluation of patients with known MS with changing symptoms or signs.	I
5. Assessment of hemodynamic response of mean gradient and pulmonary artery pressures by exercise Doppler echocardiography in patients when there is a discrepancy between resting hemodynamics and clinical findings.	IIa
6. Reevaluation of asymptomatic patients with moderate to severe MS to assess pulmonary artery pressure.	IIb
7. Routine reevaluation of the asymptomatic patient with mild MS and stable clinical findings.	III

Recommendations for Transesophageal Echocardiography in Mitral Stenosis

Indication	*Class*
1. Assess for presence or absence of left atrial thrombus in patients being considered for percutaneous mitral balloon valvotomy or cardioversion.	IIa
2. Evaluate mitral valve morphology and hemodynamics when transthoracic echocardiography provides suboptimal data.	IIa
3. Routine evaluation of mitral valve morphology and hemodynamics when complete transthoracic echocardiographic data are satisfactory.	III

In the patient who presents with asymptomatic MS, an initial clinical history, physical examination, ECG, and chest x-ray should be performed. 2-D and Doppler echocardiography should also be performed to confirm the diagnosis of MS and rule out other concomitant problems that would require further therapy, ie, myocardial or other valvular heart disease. The morphology of the mitral valve apparatus should be assessed. The severity of MS should be determined by 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 >1.5 cm^2 and mean gradient <5 mm Hg), no further evaluation is needed on the initial workup (Figure 3). These patients usually remain stable for years (255,256,266). 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 and no calcification in the commissures, percutaneous mitral valvotomy can be performed with a low complication rate and may be indicated if symptoms develop. Due to the slowly progressive course of MS, patients may remain "asymptomatic" with severe stenosis merely by readjusting their lifestyle to a more sedentary level. Elevated pulmonary vascular resistance and/or low cardiac output may also play an adaptive role in preventing symptoms from occurring in patients with severe MS (260,262,263). Elevation of pulmonary vascular resistance is an important physiological event in MS (262), 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 >50 mm Hg) and pliable mitral valve 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 (286–289). Objective limitation of exercise tolerance with a rise in transmitral gradient >15 mm Hg and in pulmonary artery systolic pressure >60 mm Hg may be an indication for percutaneous valvotomy if the mitral valve morphology is suitable. There is a subset of asymptomatic patients with severe MS (valve area <1.0 cm^2) and severe pulmonary hypertension (pulmonary artery systolic pressure $>75\%$ 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 mitral valve replacement (MVR) should be performed in the absence of symptoms to prevent right ventricular failure, but surgery is generally recommended in such patients.

b. Medical Therapy: General. In the patient with MS, the major problem is mechanical obstruction to inflow at the level of the mitral valve, and no medical therapy will specifically relieve the fixed obstruction. The left ventricle 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. Infective endocarditis is uncommon but does occur in isolated MS (255,256), and appropriate endocarditis prophylaxis is also 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 mitral valve. Agents with negative chronotropic properties such as β-blockers or calcium channel blockers may be of benefit in patients in sinus rhythm who have exertional symptoms if these symptoms occur with high heart rates (291,292). 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 left and/or right ventricular dysfunction (293).

c. 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 (254,255). Structural changes from the pressure and volume overload alter the electrophysiological properties of the left atrium (266), and the rheumatic process itself may lead to fibrosis of the internodal tracts and damage to the sinoatrial node. There may be significant hemodynamic consequences resulting from the acute development of atrial fibrillation, with loss of atrial contribution to LV filling, and 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 (254) 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 (256). The risk of arterial embolization, especially stroke, is significantly increased in patients with atrial fibrillation (254,255,294–296).

Treatment of an acute episode of rapid atrial fibrillation consists of anticoagulation with heparin and control of the heart rate response. Intravenous digoxin, calcium channel blockers, or β-blockers should be used to control ventricular response by slowing conduction through the atrioventricular node. If there is hemodynamic instability, electrical cardioversion should be undertaken urgently, with intravenous heparin before, during, and after the procedure. Patients who have been in atrial fibrillation longer than 24 to 48 hours without anticoagulation are at an increased risk for embolic events after cardioversion, but embolization may occur with <24 hours 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 hours 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 ≥3 weeks, followed by elective cardioversion (297). 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 (298). It is important to continue anticoagulation after cardioversion to prevent thrombus formation due to atrial mechanical inactivity and then continue long-term warfarin.

Recurrent paroxysmal atrial fibrillation may be treated with antiarrhythmic drugs consisting of group IC agents, group IA agents (in conjunction with a negative dromotropic agent), or amiodarone to try to prevent further episodes. Eventually, atrial fibrillation becomes resistant to prevention or cardioversion (266), and control of ventricular response becomes the mainstay of therapy. Digoxin slows the heart rate response in patients with atrial fibrillation and MS (293). However, calcium channel blockers or β-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 (295,299). 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.

d. Medical Therapy: Prevention of Systemic Embolization. Systemic embolization may occur in 10% to 20% of patients with MS (254,255,294). The risk of embolization is related to age and the presence of atrial fibrillation (254,255,294–296). 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 (254,295,300). An embolic event may thus be the initial manifestation of MS (254). In patients who have experienced an embolic event, the frequency of recurrence is as high as 15 to 40 events per 100 patient months (295,299).

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 (295,299). This benefit applies to both systemic and pulmonary embolism. Most trials involved patients who had ≥1 embolus before the onset of anticoagulation therapy (299). 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 (301,302). In these randomized trials, the subset of patients who benefited most from anticoagulation were those with the highest risk of embolic events (301,302). 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 (254,255,294–296,299). 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 (ie, severe stenosis or an enlarged left atrium) should be considered for long-term warfarin therapy (303,304).

Although embolic events are thought to originate from left atrial thrombi (295,296), the presence or absence of a left atrial thrombus does not seem to correlate with embolic events (254,294). 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 (254,294). Thus, the decision to anticoagulate a patient with MS should not be based solely on the echocardiographic demonstration of a left atrial thrombus.

It has been suggested that surgical commissurotomy reduces the incidence of future embolic events (267). 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 (266,305,306).

Recommendations for Anticoagulation in Mitral Stenosis

Indication	*Class*
1. Patients with atrial fibrillation, paroxysmal or chronic.	I
2. Patients with a prior embolic event.	I
3. Patients with severe MS and left atrial dimension ≥55 mm by echocardiography.*	IIb
4. All other patients with MS.	III

***Based on grade C recommendation given this indication by American College of Chest Physicians Fourth Consensus Conference on Antithrombotic Therapy (303). The Working Group of the European Society of Cardiology recommended a lower threshold of left atrial dimension (>50 mm) for recommending anticoagulation (304).**

e. 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 (261,263). The long-term effects of repeated exertion-related increases in pulmonary venous and pulmonary artery pressures on the lung or right ventricle remain unknown (105). MS rarely causes sudden death (254–256). 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 26th Bethesda Conference on Recommendations for Determining Eligibility for Competition in Athletes with Cardiovascular Abnormalities has published guidelines for patients with MS who wish to engage in competitive athletics (105).

f. 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 (254,266). All patients should be informed that any change in symptoms warrants reevaluation. In the asymptomatic patient, yearly reevaluation is recommended (Figure 3). At the time of the yearly evaluation, a history, physical examination, chest x-ray, and ECG should be obtained. An echocardiogram is not recommended yearly unless there is a change in clinical status. Ambulatory ECG monitoring to detect paroxysmal atrial fibrillation is indicated in patients with palpitations.

3. Evaluation of the Symptomatic Patient. *a. Initial Workup.* Patients who develop symptoms should undergo evaluation with a history, physical examination, ECG, chest x-ray, and echocardiogram (Figures 4 and 5). 2-D and Doppler echocardiography is indicated to evaluate mitral valve morphology, mitral valve hemodynamics, and pulmonary artery pressure. Patients with NYHA functional Class II symptoms and moderate or severe stenosis (mitral valve area ≤ 1.5 cm^2 or mean gradient ≥ 5 mm Hg) may be considered for mitral balloon valvotomy if they have suitable mitral valve morphology. Patients who have NYHA functional Class III or IV symptoms and evidence of severe MS have a poor prognosis if left untreated (254–256) and should be considered for intervention with either balloon valvotomy or surgery.

A subset of patients has significant limiting symptoms yet resting hemodynamics that do not indicate moderate to severe MS. If there is a discrepancy between symptoms and hemodynamic data, 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 upright exercise with Doppler recording of TR and transmitral velocities (286–289). Right- and left-heart catheterization with exercise may also be helpful (307). Patients who are symptomatic with a significant elevation of pulmonary artery pressure (>60 mm Hg), mean transmitral gradient (>15 mm Hg), or pulmonary artery wedge pressure ($\geq$25 mm Hg) on exertion (261,286–288,308) 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 mitral valve.

b. Indications for Cardiac Catheterization. Cardiac catheterization has been considered the standard for determining the severity of MS. Direct measurements of left atrial and LV pressure determine the transmitral gradient, which is the fundamental expression of the severity of MS (259). Because the severity of obstruction is dependent on both flow and gradient (263), the hydraulic Gorlin equation has been used in the catheterization laboratory to derive a calculated valve area (106). Pulmonary artery pressures and resistance can be obtained to examine 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 (275,276). 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.

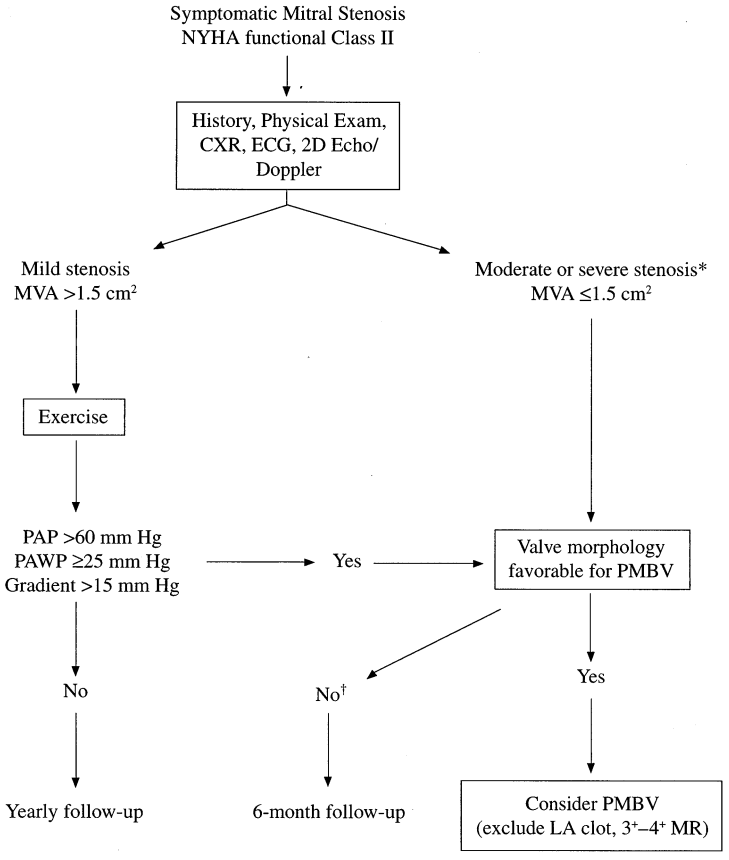

Figure 4. Management strategy for patients with mitral stenosis and mild symptoms. Abbreviations: CXR = chest x-ray, LA = left atrial, MVA = mitral valve area, PMBV = percutaneous mitral balloon valvotomy, PAP = pulmonary artery pressure, PAWP = pulmonary artery wedge pressure. *The committee recognizes that there may be variability in the measurement of MVA and that the mean transmitral gradient, PAWP, and PAP should also be taken into consideration. †There is controversy as to whether patients with severe MS (MVA <1.0 cm^2) and severe pulmonary hypertension (PAP >60–80 mm Hg) should undergo MVR to prevent right ventricular failure.

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 (309).

Mitral valve area is derived from either the half-time method or continuity equation by Doppler echocardiography. These measurements correlate well in most instances with valve areas from cardiac catheterization (281,282). The Doppler half-time method may be inaccurate if there are changes in compliance of the left atrium or left ventricle (282,283), especially after mitral balloon valvotomy, or if there is concomitant AR. There are limitations to mitral valve area calculations derived from catheter 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 (265,284). 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. 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, mitral valve 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. Catheterization including left ventriculography (to evaluate 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 VIII of these guidelines).

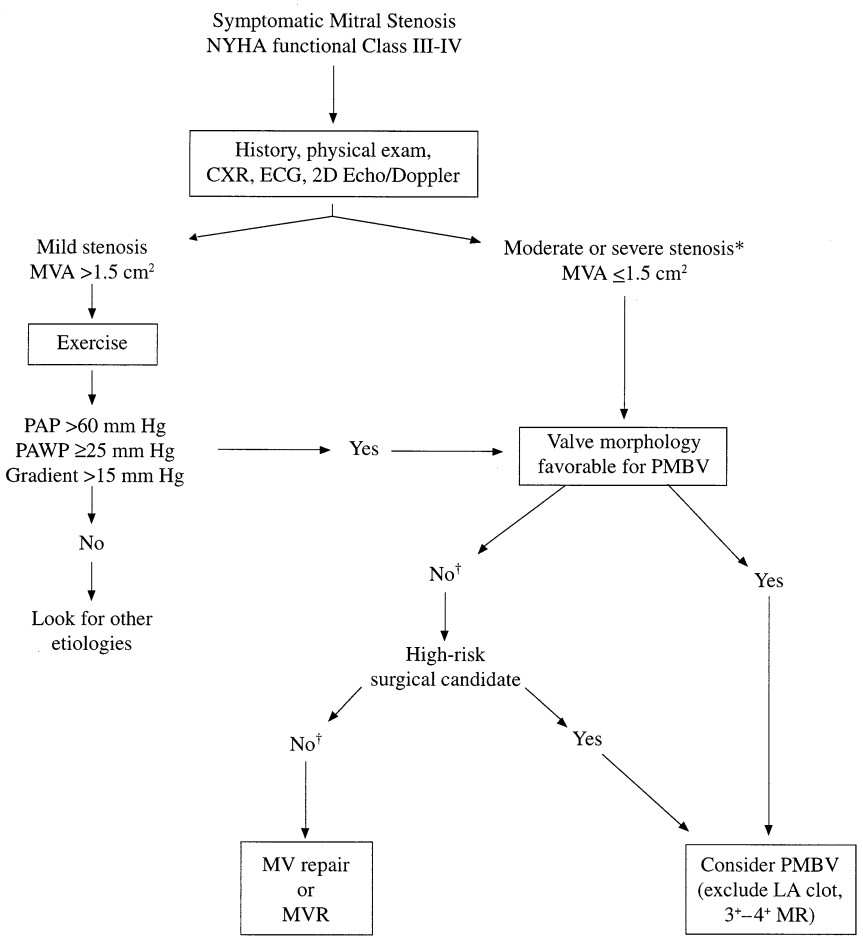

Figure 5. Management strategy for patients with mitral stenosis and moderate to severe symptoms. Abbreviations: CXR = chest x-ray, LA = left atrial, MV = mitral valve, MVA = mitral valve area, PMBV = percutaneous mitral balloon valvotomy; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure. *The committee recognizes that there may be variability in the measurement of MVA and that the mean transmitral gradient, PAWP, and PAP should also be taken into consideration. †It is controversial as to which patients with less favorable valve morphology should undergo PMBV rather than mitral valve surgery (see text).

Recommendations for Cardiac Catheterization in Mitral Stenosis

Indication	*Class*
1. Perform percutaneous mitral balloon valvotomy in properly selected patients.	**I**
2. Assess severity of MR in patients being considered for percutaneous mitral balloon valvotomy when clinical and echocardiographic data are discordant.	**IIa**
3. Assess pulmonary artery, left atrial, and LV diastolic pressures when symptoms and/or estimated pulmonary artery pressure are discordant with the severity of MS by 2-D and Doppler echocardiography.	**IIa**
4. Assess hemodynamic response of pulmonary artery and left atrial pressures to stress when clinical symptoms and resting hemodynamics are discordant.	**IIa**
5. Assess mitral valve hemodynamics when 2-D and Doppler echocardiographic data are concordant with clinical findings.	**III**

4. Indications for Surgical or Percutaneous Valvotomy. 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 in the 1960s, open mitral commissurotomy and replacement of the mitral valve became the surgical procedures of choice for the treatment of MS. Percutaneous mitral balloon valvotomy emerged in the mid 1980s. This procedure, in which one or more large balloons is inflated across the mitral valve by a catheter-based approach, has become an accepted alternative to surgical approaches in selected patients.

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 increase in the calculated mitral valve area, with resulting improvement in clinical symptomatology. The extent of hemodynamic and clinical improvement is dependent on the underlying morphology of the mitral valve apparatus. Patients with pliable, noncalcified valves and minimal fusion of the subvalvular apparatus achieve the best immediate and long-term results.

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 (310–312). Closed commissurotomy remains the surgical technique of choice in many developing countries. Open commissurotomy has now become the accepted surgical procedure in

most institutions in the United States (313–316), because it allows direct inspection of the mitral valve 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 (317). The results of the operation are dependent on the morphology of the mitral valve apparatus and the surgeon's skill and experience. In patients with marked deformity of the mitral valve apparatus, a decision for MVR can be made at the time of operation. The risk of operation is between 1% and 3%, depending on the concomitant medical status of the patient (313–316). 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 mid 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. The 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 (318). 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 (318–323). The mean valve area usually doubles (from 1.0 cm^2 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 mitral valve area >1.5 cm^2 and a decrease in left atrial pressure to ≤ 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 (>1.5:1 left-to-right shunt) occurs in $\leq 12\%$ of patients with the double balloon technique and <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 of balloon valvotomy in larger series has ranged from 1% to 2% (318–321); however, with increasing experience with the procedure, percutaneous mitral valvotomy can be done in selected patients with a mortality of <1% (322).

Follow-up information after percutaneous balloon valvotomy is limited. Event-free survival (freedom from death, repeat valvotomy, or MVR) overall is 50% to 65% over 3 to 7 years, with an event-free survival of 80% to 90% in patients with favorable mitral valve morphology (280,320,322–324). 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 (325–329). These trials, summarized in Table 16, consisted of younger patients (aged 10 to 30 years) with pliable mitral valve 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 (327,329) indicate more favorable hemodynamic and symptomatic results with percutaneous balloon valvotomy than with closed commissurotomy and results equivalent to those of open commissurotomy.

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 (320,322,323). The underlying mitral valve morphology is the factor of greatest importance in determining outcome (277–280,320,323,324,330), and immediate post-valvotomy hemodynamics are predictive of long-term clinical outcome (322). Patients with valvular calcification, 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 17). 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 (279,280). Alternatively, in patients with noncalcified pliable valves and no calcium in the commissures, the procedure can be performed with a high success rate (>90%), low complication rate (<3%), and sustained improvement in 80% to 90% over a 3- to 7-year follow-up period (280,320,322,324).

Relative contraindications to percutaneous balloon valvotomy include the presence of a left atrial thrombus and significant (3+ to 4+) MR. Transesophageal echocardiography is frequently performed 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.

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. 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 (new-onset atrial fibrillation) or pulmonary circulation (pulmonary artery

Table 16. Randomized Trials of Percutaneous Mitral Balloon Valvotomy and Surgical Commissurotomy

Study, year	Mean follow-up	Procedure	Number of patients	Age	Average score	Mitral gradient		MVA		Restenosis	Freedom from reintervention	NYHA FC I
						Pre	Post	Pre	Post			
Patel et al 1991 (325)	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 ± 4	0.7 ± 0.2	1.3 ± 0.3	—	—	—
Turi et al 1991 (328)	7 mo	PMBV	20	27 ± 8	7.2	18 ± 4	10 ± 2	0.8 ± 0.2	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 (326)	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 (327)	3 y	PMBV	30	30 ± 9	6.7	—	—	0.9 ± 0.3	2.4 ± 0.6*	10%	—	72%
		OC	30	31 ± 9	7.0	—	—	0.9 ± 0.3	1.8 ± 0.4	13%	—	57%
Ben Farhat et al 1998 (329)	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%

Abbreviations: CC = closed commissurotomy, FC = functional class, MVA = mitral valve area, NYHA = New York Heart Association, OC = open commissurotomy, PMBV = percutaneous mitral balloon valvotomy. *Significant difference ($P < 0.05$) in increased MVA by PMBV compared with surgical commissurotomy.

pressure >50 mm Hg at rest or >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 (331) (see Figure 5). Although there is a higher acute complication rate and a lower event-free survival rate (≈50% at 5 years in these patients, compared with 80% to 90% in patients with favorable valve morphology), this must be weighed against the risks and potential complications of surgical MVR.

Patients who are being considered for an intervention should undergo evaluation with a history, physical examination, and 2-D and Doppler echocardiographic examination. The appearance and mobility of the mitral valve apparatus and commissures should be evaluated by 2-D echocardiography, and the transmitral gradient, mitral valve 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 and/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 (318,321). Thus, the decision to proceed with percutaneous balloon valvotomy or surgical commissurotomy is dependent on the experience of the operator and institution. Due to 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 (Figures 3 and 4).

Table 17. Echocardiographic Prediction of Outcome of Percutaneous Mitral Balloon Valvotomy

Study, year	Mean follow-up, mo	Echo criteria	Number of patients	Age	Survival	Survival free of events	Events
Cohen et al 1992 (320)	36 ± 20	score ≤8	84	—	—	68% at 5 y	Death, MVR, repeat PMBV
		score >8	52	—	—	28% at 5 y	
Palacios et al 1995 (324)	20 ± 12	score ≤8	211	48 ± 14	98% at 4 y	98% at 4 y	Death, MVR, NYHA FC III–IV symptoms
		score >8	116	64 ± 11	72% at 4 y	39% at 4 y	
Dean et al 1996 (323)	38 ± 16	score <8	272	49 ± 13	95% at 4 y	—	Death
		score 8–12	306	58 ± 15	83% at 4 y	—	
		score >12	24	58 ± 15	24% at 4 y	—	
Cannan et al 1997 (280)	22 ± 10	Com Ca−	120	—	—	86% at 3 y	Death, MVR, repeat PMBV
		Com Ca+	29	—	—	40% at 3 y	

Abbreviations: Com Ca = commissural calcification, echo = echocardiographic, FC = functional class, MVR = mitral valve replacement, NYHA = New York Heart Association, PMBV = percutaneous mitral balloon valvotomy.

Recommendations for Percutaneous Mitral Balloon Valvotomy

Indication	*Class*
1. Symptomatic patients (NYHA functional Class II, III, or IV), moderate or severe MS (mitral valve area ≤1.5 cm^2),* and valve morphology favorable for percutaneous balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR.	I
2. Asymptomatic patients with moderate or severe MS (mitral valve area ≤1.5 cm^2)* and valve morphology favorable for percutaneous balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR.	IIa
3. Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),* and a nonpliable calcified valve who are at high risk for surgery in the absence of left atrial thrombus or moderate to severe MR.	IIa
4. Asymptomatic patients, moderate or severe MS (mitral valve area ≤1.5 cm^2)* and valve morphology favorable for percutaneous balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR.	IIb
5. Patients in NYHA functional Class III-IV, moderate or severe MS (MVA ≤1.5 cm^2), and a nonpliable calcified valve who are low-risk candidates for surgery.	IIb
6. Patients with mild MS.	III

*The committee recognizes that there may be variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure at rest or during exercise should also be taken into consideration.

Recommendations for Mitral Valve Repair for Mitral Stenosis

Indication	*Class*
1. Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),* and valve morphology favorable for repair if percutaneous mitral balloon valvotomy is not available.	I
2. Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),* and valve morphology favorable for repair if a left atrial thrombus is present despite anticoagulation.	I
3. Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area ≤1.5 cm^2),* and a nonpliable or calcified valve with the decision to proceed with either repair or replacement made at the time of the operation.	I
4. Patients in NYHA functional Class I, moderate or severe MS (mitral valve area ≤1.5 cm^2),* and valve morphology favorable for repair who have had recurrent episodes of embolic events on adequate anticoagulation.	IIb
5. Patients with NYHA functional Class I-IV symptoms and mild MS.	III

*The committee recognizes that there may be a variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure at rest or during exercise should also be considered.

5. Indications for Mitral Valve Replacement. MVR is an accepted surgical procedure for patients with severe MS who are not candidates for surgical commissurotomy or percutaneous mitral valvotomy. The risk of MVR is dependent on multiple factors, including functional status, age, LV function, cardiac output, concomitant medical problems, and concomitant CAD. In the young, healthy person, MVR can be performed with a risk of <5%. However, in the older patient with concomitant medical problems or pulmonary hypertension at systemic levels, the risk of MVR may be as high as 10% to 20%. Complications of MVR include valve thrombosis, valve dehiscence, valve infection, valve malfunction, and embolic events. These are discussed in detail in section VII of these guidelines. There is also the known risk of long-term anticoagulation.

If there is significant calcification, fibrosis, and subvalvular fusion of the mitral valve apparatus, commissurotomy or percutaneous balloon valvotomy is less likely to be successful, and MVR will be necessary. Given the risk of MVR and the potential long-term complications of a prosthetic valve, there are stricter indications for mitral valve 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, MVR 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 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 <1 cm^2) and severe pulmonary hypertension (pulmonary artery systolic pressure >60 to 80 mm Hg) should undergo MVR to prevent right ventricular failure, but surgery is generally recommended in such patients. It is recognized that patients with such severe pulmonary hypertension are rarely asymptomatic.

Recommendations for Mitral Valve Replacement for Mitral Stenosis

Indication	*Class*
1. Patients with moderate or severe MS (mitral valve area ≤1.5 cm^2)* and NYHA functional Class III-IV symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair.	I
2. Patients with severe MS (mitral valve area ≤1 cm^2)* and severe pulmonary hypertension (pulmonary artery systolic pressure >60 to 80 mm Hg) with NYHA functional Class I-II symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair.	IIa

*The committee recognizes that there may be a variability in the measurement of mitral valve area and that the mean transmitral gradient, pulmonary artery wedge pressure, and pulmonary artery pressure should also be considered.

6. Management of Patients After Valvotomy or Commissurotomy. Symptomatic improvement occurs immediately after successful percutaneous balloon valvotomy or surgical commissurotomy, although objective measurement of maximum oxygen consumption may continue to improve over several months postoperatively due to slowly progressive im-

provement in skeletal muscle metabolism (332). 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 (333–336). Gradual regression of pulmonary hypertension over months has been demonstrated (333,334,336).

Recurrent symptoms after successful surgical commissurotomy have been reported to occur in as many as 60% of patients after 9 years (285,310,337). However, recurrent stenosis accounts for symptoms in <20% of patients (337). In patients with an adequate initial result, progressive MR and development of other valvular or coronary problems are more frequently responsible for recurrent symptoms (337). Thus, in patients presenting with symptoms late after commissurotomy, a comprehensive evaluation is required to look for other causes. Patients undergoing percutaneous mitral valvotomy have a higher incidence of recurrent symptoms at 1- to 2-year follow-up if there was an unfavorable mitral valve morphology, due to either an initial inadequate result or restenosis (338).

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 as well as 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 hours 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 (282,283). Patients with severe MR or a large atrial septal defect should be considered for early operation. 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. Prophylaxis against infective endocarditis and recurrence of rheumatic fever 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 2-D and Doppler echocardiography should be performed to evaluate the mitral valve hemodynamics and pulmonary artery pressure as well as 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 balloon valvotomy (277,339). The results of these procedures are less satisfactory than the overall results of initial valvotomy because there is usually more valve deformity, calcification, and fibrosis than with the initial procedure (277,339). MVR should be considered in those patients with recurrent severe symptoms and severe deformity of the mitral apparatus.

7. Special Considerations. *a. 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 V of these guidelines.

b. 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 (269,270). Older patients are more likely to have heavy calcification and fibrosis of the mitral valve leaflets, with significant subvalvular fusion. In patients older than 65, the success rate of percutaneous valvotomy is lower (<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 (270).

D. Mitral Valve Prolapse

1. Pathophysiology and Natural History. MVP refers to a systolic billowing of one or both mitral leaflets into the left atrium with or without MR. It is the most common form of valvular heart disease and occurs in 2% to 6% of the population. MVP often occurs as a clinical entity with little or no MR but is also the most common cause of significant MR in the United States. MR stemming from MVP is frequently associated with unique clinical characteristics when compared with other causes of MR (340,341).

The mitral valve apparatus is a complex structure composed of the mitral annulus; valve leaflets; chordae tendineae; papillary muscles; and the supporting LV, left atrial, and aortic walls (342). Disease processes involving any of these components may result in dysfunction of the valve apparatus and prolapse of the mitral leaflets toward the left atrium during systole, when LV pressure exceeds left atrial pressure. A classification of MVP is shown in Table 18 (343,344).

In primary MVP, there is interchordal hooding due to leaflet redundancy that includes both the rough and clear zones of the involved leaflets (345). The height of the interchordal hooding is usually >4 mm and involves at least one half of the anterior leaflet or two thirds of the posterior leaflet. 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 forming the atrial aspect of the leaflet) and the fibrosa or ventricularis (dense layers of collagen that form the basic support of the leaflet). In primary MVP, 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 surfaces of the mitral valve leaflets, thinning and/or elongation

Table 18. Classification of Mitral Valve Prolapse

Primary MVP
Familial
Nonfamilial
Marfan's syndrome
Other connective tissue diseases
Secondary MVP
CAD
Rheumatic heart disease
Reduced LV dimensions*
Hypertrophic cardiomyopathy
Atrial septal defect
Pulmonary hypertension
Anorexia nervosa
Dehydration
Straight-back syndrome/pectus excavatum
"Flail" mitral valve leaflet(s)
Normal variant
Inaccurate auscultation
"Echocardiographic heart disease"

Adapted from O'Rourke RA (343). The mitral valve prolapse syndrome. In: Chizner MA, ed. *Classic Teachings in Clinical Cardiology*: *A Tribute to W Proctor Harvey, M.D.* New Jersey: Laennec Publ Co; 1996:1049–1070. *From Levine HJ, Isner JM, Salem DN (344). Primary versus secondary mitral valve prolapse: clinical features and implications. Clin Cardiol. 1982;5:371–375.

of chordae tendineae, and ventricular friction lesions. Fibrin deposits often form at the mitral valve–left atrial angle.

The primary form of MVP usually occurs as isolated cases but may be familial and transmitted as an autosomal dominant trait (346,347). It occurs with increased frequency in patients with Marfan syndrome and in other connective tissue diseases (345,348–350). It has been speculated that the primary MVP syndrome represents a generalized disease of connective tissue. Thoracic skeletal abnormalities such as a straight thoracic spine and pectus excavatum are commonly associated with MVP (351). The increased incidence of primary MVP in patients with von Willebrand's disease and other coagulopathies, primary hypomastia, and various connective tissue diseases has been used to support the concept that MVP is a result of defective embryogenesis of cell lines of mesenchymal origin (352).

Secondary forms of MVP occur in which myxomatous proliferation of the spongiosa portion of the mitral valve leaflet is absent. Serial studies in patients with known ischemic heart disease have occasionally documented unequivocal MVP after an acute coronary syndrome that was previously absent (353–355). In most patients with CAD and MVP, however, the 2 entities are coincident but unrelated.

Several recent studies indicate that valvular regurgitation caused by MVP may result from postinflammatory changes, including those after rheumatic fever (356–358). In histological studies of surgically excised valves, fibrosis with vascularization and scattered infiltration of round cells including lymphocytes and plasmacytes were found without myxomatous proliferation of the spongiosa. With rheumatic carditis the anterior mitral leaflet is more likely to prolapse.

MVP has been observed in patients with hypertrophic cardiomyopathy in whom posterior MVP may result from a disproportionally small LV cavity, altered papillary muscle alignment, or a combination of factors (359). The mitral valve leaflet is usually normal. MVP may occur secondary to ruptured chordae tendineae as a "flail" or partial flail mitral leaflet, whether spontaneous or due to infective endocarditis.

Patients with primary and secondary MVP must be distinguished from normal variants by cardiac auscultation and/or echocardiography; these variations can result in an incorrect diagnosis of MVP, particularly in patients whose hearts are hyperkinetic or who are dehydrated (360). Other auscultatory findings may be misinterpreted as midsystolic clicks or late systolic murmurs. Patients with mild to moderate billowing of one or both nonthickened leaflet(s) toward the left atrium with the leaflet coaptation point on the LV side of the mitral annulus and with minimal or no MR by Doppler echocardiography are probably normal (361). Unfortunately, many such patients are overdiagnosed as having the MVP syndrome.

In patients with MVP, there may be left atrial dilatation and LV enlargement, depending on the presence and severity of MR. The supporting apparatus is often involved, and in patients with connective tissue syndromes such as Marfan syndrome, the mitral annulus is usually dilated and sometimes calcified and does not decrease its circumference by the usual 30% during LV systole.

Many studies suggest autonomic nervous system dysfunction in many patients with primary MVP. In several studies, measurements of serum and 24-hour urine epinephrine or norepinephrine levels were increased in patients with symptomatic MVP compared with age-matched controls (362–365).

Tricuspid valve prolapse with similar interchordal hooding and histological evidence of mucopolysaccharide proliferation and collagen dissolution occurs in ≈40% of patients with MVP (346). Pulmonic valve prolapse and aortic valve prolapse occur in ≈10% and 2% of patients with MVP, respectively (345). There is an increased incidence of secundum atrial septal defect in patients with MVP as well as an increased incidence of left-sided atrioventricular bypass tracts and supraventricular arrhythmias (345).

In most patient studies, the MVP syndrome is associated with a benign prognosis (366,367). The age-adjusted survival rate of both men and women with MVP is similar to that of individuals without this common clinical entity (346). 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 development of congestive heart failure (340). Pulmonary hypertension may occur with associated right ventricular 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 LV dysfunction, atrial fibrillation, and in certain instances ruptured mitral valve chordae (340).

Several long-term prognostic studies suggest that complica-

tions occur most commonly in patients with a mitral systolic murmur, those with thickened redundant mitral valve leaflets, and those with increased LV or left atrial size, especially in men older than 45 years (340,368–372).

Sudden death is a rare complication of MVP occurring in <2% of known cases during long-term follow-up (366–373), with annual mortality rates <1% per year. The likely cause is a ventricular tachyarrhythmia based on the finding of an increased incidence of complex ventricular ectopy on ambulatory ECG recordings in patients with MVP who had sudden cardiac death (374,375). Although infrequent, the highest incidence of sudden death has been reported in the familial form of MVP; some of these patients have also been noted to have QT prolongation (340,376).

Infective endocarditis is a serious complication of MVP, which is the leading predisposing cardiovascular diagnosis in most series of patients reported with endocarditis (340,350,377). Because the absolute incidence of endocarditis is extremely low for the entire MVP population, there has been much controversy about the risk of endocarditis in MVP (378).

As indicated above, progressive MR occurs frequently in patients with long-standing MVP. Fibrin emboli are responsible in some patients for visual symptoms consistent with involvement of the ophthalmic or posterior cerebral circulation (379). Several studies have indicated an increased likelihood of cerebrovascular accidents in patients under age 45 who have MVP over what would have been expected in a similar population without MVP (380).

2. Evaluation and Management of the Asymptomatic Patient. The diagnosis of MVP is most commonly made by cardiac auscultation in asymptomatic patients or echocardiography performed for another purpose. The patient may be evaluated because of a family history of cardiac disease or occasionally may be referred because of an abnormal resting ECG.

The primary diagnostic evaluation of the patient with MVP is a careful physical examination (340,381). The principal cardiac 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 mitral valve apparatus as the leaflets prolapse into the left atrium during systole. The midsystolic click(s) is frequently followed by a late systolic murmur, 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 also vary under certain conditions, from brief and almost inaudible to holosystolic and loud. Dynamic auscultation is often useful for establishing the clinical diagnosis of the MVP syndrome (381). 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), the critical volume is achieved earlier in systole and the click-murmur complex occurs shortly after the first heart sound. By contrast, any maneuver that augments the volume of blood in the ventricle (eg, squatting), reduces myocardial contractility, or increases LV afterload lengthens the time from onset of systole to initiation of MVP, and the systolic click and/or murmur move toward the second heart sound.

Although the ECG may provide some information in patients with MVP, it is most often normal. Nonspecific ST-T wave changes, T-wave inversions, prominent U 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 abnormalities.

Posterior-anterior and lateral chest roentgenograms usually show normal cardiopulmonary findings. The skeletal abnormalities described above, such as pectus excavatum, are often seen (351). When severe MR is present, both left atrial and LV enlargement often result. Various degrees of pulmonary venous congestion are evident when left-heart failure results. Calcification of the mitral annulus may be seen, particularly in adults with Marfan syndrome (381). In asymptomatic patients with MVP, a chest x-ray usually provides no additional information.

2-D and Doppler echocardiography is the most useful noninvasive test for defining MVP. The M-mode echocardiographic definition of MVP includes ≥2 mm posterior displacement of one or both leaflets or holosystolic posterior "hammocking" >3 mm. On 2-D echocardiography, systolic displacement of one or both mitral leaflets in the parasternal long-axis view, particularly when they coapt on the atrial side of the annular plane, indicates a high likelihood of MVP. There is disagreement concerning the reliability of echocardiographic diagnosis of MVP when observed in only the apical 4-chamber view (382,383). The diagnosis of MVP is even more certain when the leaflet thickness is >5 mm. Leaflet redundancy is often associated with an enlarged mitral annulus and elongated chordae tendineae (340). On Doppler echocardiography, the presence or absence of MR is an important consideration, and MVP is more likely when MR is detected as a high-velocity eccentric jet in late systole (361).

At present, there is no consensus on the 2-D echocardiographic criteria for MVP. Because echocardiography is a tomographic cross-sectional technique, no single view should be considered diagnostic. The parasternal long-axis view permits visualization of the medial aspect of the anterior mitral leaflet and middle scallop of the posterior leaflet. If the findings of prolapse are localized to the lateral scallop in the posterior leaflet, they would be best visualized by the apical 4-chamber view. All available echocardiographic views should be used with the provision that billowing of the anterior leaflet alone in the 4-chamber apical view is not evidence of prolapse; however, a displacement of the posterior leaflet or the coaptation point in any view, including the apical view, suggests the diagnosis of prolapse. The echocardiographic criteria for MVP

should include structural changes such as leaflet thickening, redundancy, annular dilatation, and chordal elongation.

Patients with echocardiographic evidence for MVP but without evidence of thickened/redundant leaflets or definite MR are more difficult to classify. If such patients have clinical auscultatory findings of MVP, then the echocardiogram usually confirms the diagnosis.

Recommendations for Echocardiography in Mitral Valve Prolapse*

Indication	*Class*
1. Diagnosis, assessment of hemodynamic severity of MR, leaflet morphology, and ventricular compensation in patients with physical signs of MVP.	I
2. To exclude MVP in patients who have been given the diagnosis when there is no clinical evidence to support the diagnosis.	I
3. To exclude MVP in patients with first-degree relatives with known myxomatous valve disease.	IIa
4. Risk stratification in patients with physical signs of MVP or known MVP.	IIa
5. To exclude MVP in patients in the absence of physical findings suggestive of MVP or a positive family history.	III
6. Routine repetition of echocardiography in patients with MVP with mild or no regurgitation and no changes in clinical signs or symptoms.	III

*From the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2).

Although the echocardiogram is a confirmatory test for diagnosing MVP, it is not always abnormal. Nevertheless, echocardiography is useful for defining left atrial size, LV size and function, and the extent of mitral leaflet redundancy for detecting patients at high risk for complications and for detecting associated lesions such as secundum atrial septal defect. Doppler echocardiography is helpful for detection and semiquantitation of MR. Although there is controversy concerning the need for echocardiography in patients with classic auscultatory findings of MVP, the usefulness of echocardiography for risk stratification in patients with MVP has been demonstrated in ≥6 published studies (Table 19) (368,382, 384–387). All patients with MVP should have an initial echocardiogram. Serial echocardiograms are not usually necessary in the asymptomatic patient with MVP unless there are clinical indications of severe or worsening MR.

The use of echocardiography as a screening test for MVP in patients with and without symptoms who have no systolic click or murmur on serial, carefully performed auscultatory examinations is not recommended. The likelihood of finding a prolapsing mitral valve in such patients is extremely low. Most patients with or without symptoms who have a negative dynamic cardiac auscultation and "mild MVP" by echocardiography should not be diagnosed as having MVP.

Reassurance is a major part of the management of patients with MVP, most of whom are asymptomatic or have no cardiac symptoms and lack a high-risk profile. These 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 (340,381).

Antibiotic prophylaxis for the prevention of infective endocarditis during procedures associated with bacteremia is recommended for most patients with a definite diagnosis of MVP (388) as indicated in section II.B. of these guidelines. There has been some disagreement concerning whether patients with an isolated systolic click and no systolic murmur should undergo endocarditis prophylaxis. Patients with only a systolic click who have echocardiographic evidence of a higher-risk profile for endocarditis, such as leaflet thickening, elongated chordae, left atrial enlargement, or LV dilatation, should receive endocarditis prophylaxis (368,382,384–387).

Recommendations for Antibiotic Endocarditis Prophylaxis for Patients With Mitral Valve Prolapse Undergoing Procedures Associated With Bacteremia*

Indication	*Class*
1. Patients with characteristic systolic click-murmur complex.	I
2. Patients with isolated systolic click and echocardiographic evidence of MVP and MR.	I
3. Patients with isolated systolic click, echocardiographic evidence of high-risk MVP.	IIa
4. Patients with isolated systolic click and equivocal or no evidence of MVP.	III

*These procedures are listed in Tables 4 and 5.

3. Evaluation and Management of the Symptomatic Patient. Some patients consult their physicians about one 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 (340). 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 (380,389–391).

The roles of cardiac auscultation and echocardiography in the assessment of symptomatic patients with MVP are the same as for patients without symptoms. The indications for antibiotic prophylaxis to prevent endocarditis are also unchanged.

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 β-blockers (392). In many cases, however, the cessation of stimulants such as caffeine, alcohol, and 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 (eg,

Table 19. Use of Echocardiography for Risk Stratification in Mitral Valve Prolapse

Study, year	Number of patients	Features examined	Outcome	P value
Nishimura et al 1985 (368)	237	MV leaflet ≥5 mm	↑ sum of sudden death, endocarditis, and cerebral embolus	P < 0.02
		LVID ≥60 mm	↑ MVR (26% vs 3.1%)	P < 0.001
Zuppiroli et al 1994 (384)	119	MV leaflet >5 mm	↑ complex ventricular arrhythmia	P < 0.001
Babuty et al 1994 (385)	58	undefined MV thickening	no relation to complex ventricular arrhythmias	NS
Takamoto et al 1991 (386)	142	MV leaflet ≥3 mm, redundant, low echo density	↑ ruptured chordae (48% vs 5%)	
Marks et al 1989 (382)	456	MV leaflet ≥5 mm	↑ endocarditis (3.5% vs 0%)	P < 0.02
			↑ moderate-severe MR (11.9% vs 0%)	P < 0.001
			↑ MVR (6.6% vs 0.7%)	P < 0.02
			↑ stroke (7.5% vs 5.8%)	NS
Chandraratna et al 1984 (387)	86	MV leaflets >5.1 mm	↑ cardiovascular abnormalities (60% vs 6%) (Marfan syndrome, TVP, MR, dilated ascending aorta)	P < 0.001

Abbreviations: MV = mitral valve, LVID = left ventricular internal diameter, MVR = mitral valve replacement, MR = mitral regurgitation, TVP = tricuspid valve prolapse. From the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2).

aborted sudden death, recurrent syncope of unknown cause, and symptomatic or sustained ventricular tachycardia) (393).

Cardiac catheterization is not required for the diagnosis of MVP. It is helpful in evaluating associated conditions (eg, CAD and atrial septal defect) and may be needed to assess the hemodynamic effects of severe MR (as well as coronary artery anatomy) before consideration for valve repair or replacement.

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 wearing support stockings may be beneficial.

Daily aspirin therapy (80 to 325 mg/d) is recommended for MVP patients with documented focal neurological events who are in sinus rhythm with no atrial thrombi. Such patients also should avoid cigarettes and oral contraceptives. Long-term anticoagulation therapy with warfarin is recommended for post-stroke patients with MVP and MVP patients with recurrent transient ischemic attacks on aspirin therapy (INR 2 to 3). In MVP patients with atrial fibrillation, warfarin therapy is indicated in patients aged ≥65 years and those with MR, hypertension, or a history of heart failure (INR 2 to 3). Aspirin therapy is satisfactory in patients with atrial fibrillation who are <65 years, have no MR, and have no history of hypertension or heart failure (394,395). Daily aspirin therapy is often recommended for patients with high-risk echocardiographic characteristics.

Recommendations for Aspirin and Oral Anticoagulants in Mitral Valve Prolapse

Indication	*Class*
1. Aspirin therapy for cerebral transient ischemic attacks.	**I**
2. Warfarin therapy for patients aged ≥65 years, in atrial fibrillation with hypertension, MR murmur, or history of heart failure.	**I**
3. Aspirin therapy for patients aged <65 years in atrial fibrillation with no history of MR, hypertension, or heart failure.	**I**
4. Warfarin therapy for poststroke patients.	**I**
5. Warfarin therapy for transient ischemic attacks despite aspirin therapy.	**IIa**
6. Aspirin therapy for poststroke patients with contraindications to anticoagulants.	**IIa**
7. Aspirin therapy for patients in sinus rhythm with echocardiographic evidence of high-risk MVP.	**IIb**

A normal lifestyle and regular exercise are encouraged for most patients with MVP, especially those who are asymptomatic (370,396). Restriction from competitive sports is recommended when moderate LV enlargement, LV dysfunction, uncontrolled tachyarrhythmias, long QT interval, unexplained syncope, prior sudden death, or aortic root enlargement is present individually or in combination (340). 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 obtained only in patients who have high-risk characteristics on the initial echocardiogram and those who develop symptoms consistent with cardiovascular disease or have a change in physical findings suggesting development of significant MR. Patients who have high-risk characteristics, including those with moderate to severe MR, should be followed once a year.

Patients with severe MR with symptoms and/or impaired LV systolic function require cardiac catheterization and evaluation for mitral valve surgery. The thickened, redundant mitral valve can often be repaired rather than replaced with a low operative mortality and excellent short- and long-term results (391–393,397,398). Follow-up studies also suggest lower thrombotic and endocarditis risk with valve repair than with prosthetic valves.

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 mitral valve repair, especially when the posterior leaflet of the mitral valve is predominantly affected. 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 mitral valve surgery. Recommendations for surgery in patients with MVP and MR are the same as for those with other forms of nonischemic severe MR, as indicated in section III.E.4. of these guidelines.

E. Mitral Regurgitation

1. Etiology. The common etiologies for MR include MVP syndrome, rheumatic heart disease, CAD, infective endocarditis, and collagen vascular disease. Recently, anorectic drugs have also been reported to cause MR (see section III.H. of these guidelines). In some cases, such as ruptured chordae tendineae 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.

2. Acute Severe Mitral Regurgitation.

a. Pathophysiology. In acute severe MR, a sudden volume overload is imposed on the left ventricle. Acute volume overload increases LV preload, allowing for a modest increase in total LV stroke volume (399). 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, resulting 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 mitral valve repair or replacement must often be performed urgently.

b. Diagnosis. The patient with acute severe MR is almost always 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, which may or may not be holosystolic, and a third heart sound may be the only abnormal physical findings present. A fourth heart sound is also common in acute MR because the patient is usually still in sinus rhythm. Transthoracic echocardiography may demonstrate the disruption of the mitral valve and help provide semiquantitative information on lesion severity. However, transthoracic echocardiography may underestimate lesion severity by inadequate imaging of the color flow jet. Because transesophageal echocardiography can more accurately assess the color flow jet (400), transesophageal imaging should be performed if mitral valve morphology and regurgitant severity are still in question after transthoracic echocardiography. Transesophageal echocardiography is also helpful in demonstrating the anatomic cause of MR and directing successful surgical repair. Indeed, assessment of valve anatomy is a major goal of transesophageal imaging.

If ischemia is not the cause of MR and there is no reason to suspect CAD, mitral valve repair can usually be performed without the need for cardiac catheterization. However, if CAD is suspected or there are risk factors for CAD (see Section VIII. B.), coronary arteriography is necessary before surgery because myocardial revascularization should be performed during mitral valve surgery in those patients with concomitant CAD (401,402).

c. Medical Therapy. In acute severe MR, 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 mitral valve competence as LV size diminishes (403,404). 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 preparing for surgery. If infective endocarditis is the cause of acute MR, identification and treatment of the infectious organism are essential.

3. Chronic Asymptomatic Mitral Regurgitation.

a. Pathophysiology. In chronic severe MR, there has been time for development of eccentric cardiac hypertrophy in which new sarcomeres are laid down in series, increasing the length of individual myocardial fibers (153,399). The resulting increase in LV end-diastolic volume is compensatory because it permits an increase in total stroke volume, allowing for restoration of forward cardiac output (405). 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, resulting in a large total stroke volume and a normal forward stroke volume.

The duration of 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 loading conditions often maintain ejection fraction in the low normal range (0.50 to 0.60) despite the presence of significant muscle dysfunction (399,406,407).

Correction of MR should occur before the advanced phases of LV decompensation.

b. Diagnosis. In evaluating the patient with chronic MR, a careful 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 is usually present and does not necessarily indicate heart failure. Findings consistent with pulmonary hypertension are worrisome because they indicate advanced disease with worsened prognosis (408). An ECG and chest x-ray are useful in establishing rhythm and heart size, respectively. An initial echocardiogram including Doppler interrogation of the mitral valve is indispensable in the management of the patient with MR. The echocardiogram provides a baseline estimation of LV and left atrial volume, an estimation of LV ejection fraction, and approximation of the severity of regurgitation. Changes from these baseline values are subsequently used to guide the timing of mitral valve surgery. In addition, the echocardiogram can often disclose the anatomic cause of the patient's condition. In the presence of even mild TR, interrogation of the tricuspid valve yields an estimate of pulmonary artery pressure by measurement of the gradient from the right ventricle to the right atrium (409).

In some patients, Doppler studies show that MR worsens with exercise, possibly reconciling exercise-induced symptoms with resting echocardiograms that show only mild or moderate regurgitation (410).

c. 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 regurgitation has worsened. In patients with moderate MR, clinical evaluations should be performed annually, and echocardiograms are not necessary more than once per year.

Asymptomatic patients with severe MR should be followed with history, physical examination, and echocardiography every 6 to 12 months to assess symptoms or transition to asymptomatic LV dysfunction. Serial chest x-rays and ECGs have less value but are helpful in selected patients. 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.

Assessment of LV function 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 indicated that the preoperative ejection fraction is an important predictor of postoperative survival in patients with chronic MR (406,408,411,412). Ejection fraction in a patient with MR with normal LV function is usually ≥ 0.60. Consistent with this concept, postoperative survival is reduced in patients with a preoperative ejection fraction <0.60 compared with patients with higher ejection fractions (412).

Alternatively or in concert, echocardiographic LV end-systolic dimension (or volume) can be used in the timing of mitral valve surgery. End-systolic dimension, which may be less load-dependent than ejection fraction (413), should be <45 mm preoperatively to ensure normal postoperative LV function (405,413). If patients become symptomatic, they should undergo mitral valve surgery even if LV function is normal.

Recommendations for Transthoracic Echocardiography in Mitral Regurgitation

Indication	*Class*
1. For baseline evaluation to quantify severity of MR and LV function in any patient suspected of having MR.	I
2. For delineation of mechanism of MR.	I
3. For annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic severe MR.	I
4. To establish cardiac status after a change in symptoms.	I
5. For evaluation after MVR or mitral valve repair to establish baseline status.	I
6. Routine follow-up evaluation of mild MR with normal LV size and systolic function.	III

Recommendations for Transesophageal Echocardiography in Mitral Regurgitation

Indication	*Class*
1. Intraoperative transesophageal echocardiography to establish the anatomic basis for MR and to guide repair.	I
2. For evaluation of MR patients in whom transthoracic echocardiography provides nondiagnostic images regarding severity of MR, mechanism of MR, and/or status of LV function.	I
3. In routine follow-up or surveillance of patients with native valve MR.	III

d. 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 26th Bethesda Conference (105). Asymptomatic patients with MR in sinus rhythm who have normal LV volumes may exercise without restriction (105). For mildly symptomatic patients, those with LV dilatation or atrial fibrillation, exercise should be limited to activities with low to moderate dynamic and low to moderate static cardiovascular demands (105).

e. 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 and chronic AR, 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 (155,405,414,415), drugs that reduce afterload might produce a physiological state of chronic low afterload with which there is very little experience. However, in patients with MR resulting from increased preload (ie, CAD or dilated cardiomyopathy), there is reason to believe that preload reduction may be beneficial (223), and in a small series of patients with chronic MR in NYHA functional Class I to III, 1 year of quinapril therapy reduced LV volumes and mass and improved functional class (416). These data do not appear to be applicable to asymptomatic patients. Thus, in the absence of systemic hypertension, there is no known indication for the use of vasodilating drugs in asymptomatic patients with preserved LV function.

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 digitalis, rate-lowering calcium channel blockers, β-blockers, or, rarely, amiodarone. Although the risk of embolism with the combination of MR and atrial fibrillation was formerly considered similar to that of MS and atrial fibrillation, more recent studies suggest that embolic risk may be less in MR (417,418). Although this suggests that the intensity of anticoagulation in such patients can probably be reduced, firm guidelines are not yet established, and it is recommended that the INR be maintained at 2 to 3 in this population.

f. Indications for Cardiac Catheterization. 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 where 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 (advanced age, hypercholesterolemia, hypertension, etc) or when there is a suspicion that MR is ischemic in etiology (either because of known myocardial infarction or suspected ischemia), coronary angiography should be performed before surgery. In cases in which no reasonable suspicion of CAD exists, coronary angiography can be avoided.

Obviously, patients should not undergo valve surgery unless the valve lesion is severe. In cases of chronic MR, noninvasive imaging should demonstrate anatomic disruption of the valve or its apparatus, and color flow Doppler should indicate severe MR. Both the left atrium and left ventricle should be enlarged. Discordance between chamber enlargement and the presumed severity of regurgitation (ie, supposedly chronic severe MR without cardiac enlargement) raises questions about the accuracy of the diagnosis. Such questions should be resolved during ventriculography at cardiac catheterization. Although the standard semiquantitative approach to determining the severity of MR from ventriculography has its own limitations (419), ventriculography does provide an additional method to assess LV dilatation and function and gauge the severity of MR. Exercise hemodynamics and quantitative angiography may provide additional information 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. Although much has been written about the presence of a large V wave in the pulmonary artery wedge pressure tracing, the presence or absence of a large V wave has little diagnostic impact when combined with data from the rest of the catheterization (420).

Recommendations for Coronary Angiography in Mitral Regurgitation

Indication	*Class*
1. When mitral valve surgery is contemplated in patients with angina or previous myocardial infarction.	I
2. When mitral valve surgery is contemplated in patients with ≥1 risk factor for CAD (see section VIII.B. of these guidelines).	I
3. When ischemia is suspected as an etiologic factor in MR.	I
4. To confirm noninvasive tests in patients not suspected of having CAD.	IIb
5. When mitral valve surgery is contemplated in patients aged <35 years and there is no clinical suspicion of CAD.	III

Recommendations for Left Ventriculography and Hemodynamic Measurements in Mitral Regurgitation

Indication	*Class*
1. When noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery.	I
2. When there is a discrepancy between clinical and noninvasive findings regarding severity of MR.	I
3. In patients in whom valve surgery is not contemplated.	III

4. Indications for Surgery. *a. Types of Surgery.* Three different mitral valve operations are currently used for correction of MR: mitral valve repair, MVR with preservation of part or all of the mitral apparatus, and MVR 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, mitral valve 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 removed (421–427). 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 (428). However, mitral valve repair is technically more demanding than MVR, may require longer extracorporeal circulation time, and may occasionally fail. Valve calcification, rheumatic involvement, and anterior

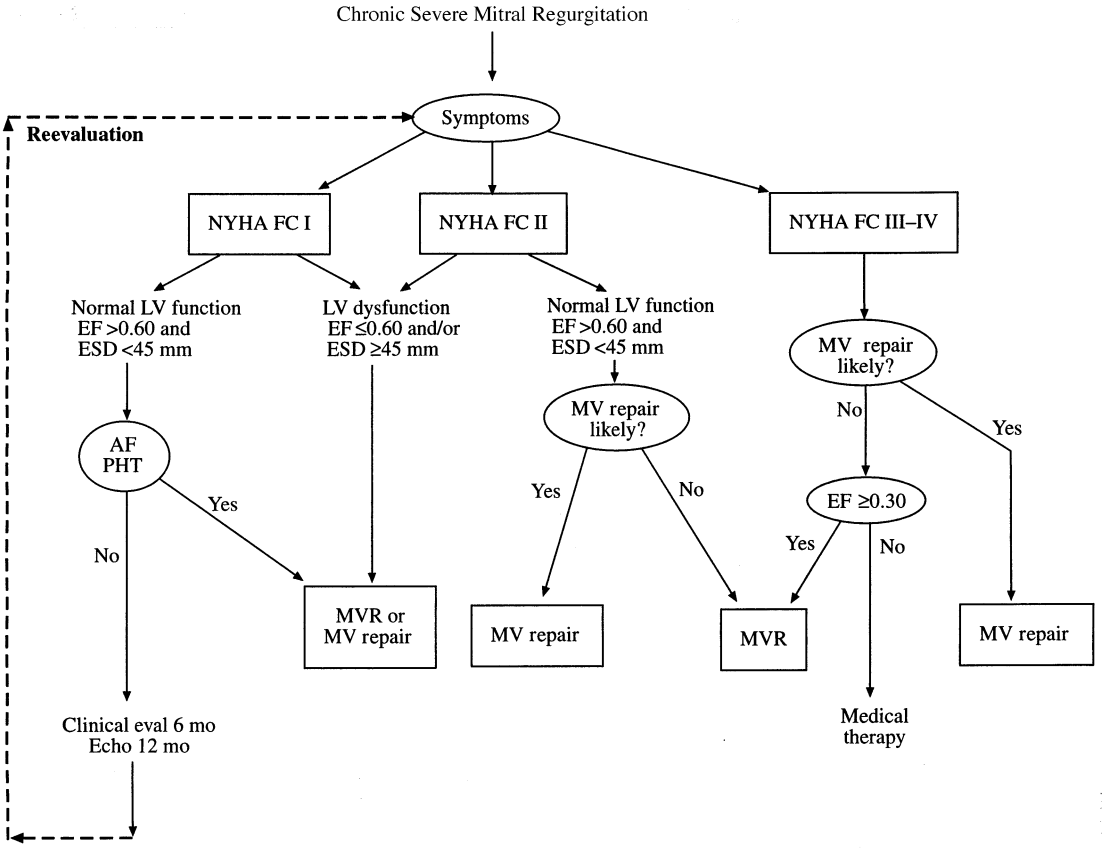

Figure 6. Management strategy for patients with chronic severe mitral regurgitation. Abbreviations: AF = atrial fibrillation, EF = ejection fraction, ESD = end-systolic diameter, FC = functional class, MV = mitral valve, NYHA = New York Heart Association, PHT = pulmonary hypertension.

leaflet involvement decrease the likelihood of repair, whereas uncalcified posterior leaflet disease is almost always reparable.

The advantage of MVR with preservation of the chordal apparatus is that this operation ensures postoperative mitral valve competence, preserves LV function, and enhances postoperative survival compared with MVR in which the apparatus is disrupted (423,429–432). 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.

MVR in which the mitral valve apparatus is destroyed 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.

The advantages of mitral valve repair make it applicable in the 2 extremes of the spectrum of MR. 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 (425); MVR 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. However, failed mitral valve repair would result in a prosthetic valve; this would represent a clear complication, as it would impose the risks of a prosthesis on a patient who did not previously require it. Hence, most cardiologists would not recommend "prophylactic" surgery in an asymptomatic patient with MR and normal LV function.

b. Timing of Surgery for Symptomatic Patients With Normal Left Ventricular Function. Patients with symptoms of congestive heart failure despite normal LV function on echocardiography (ejection fraction >0.60 and end-systolic dimension <45 mm) require surgery. Surgery should be performed in patients with mild symptoms and severe MR (Figure 6), especially if it appears that mitral valve 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, MVR with chordal preservation should relieve symptoms and maintain LV function.

c. Timing of Surgery for Asymptomatic or Symptomatic Patients With Left Ventricular Dysfunction. Preoperative variables that are predictive of postoperative survival, symptomatic

Table 20. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation

Study, year	Study design	Type of surgery	Number of patients	Outcome assessed	Findings
Schuler et al 1979 (406)	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 (411)	retrospective	MVR	105	survival	EF <0.50 predicted poor survival.
Zile et al 1984 (405)	prospective	MVR	16	heart failure, LV function	LV ESD index >2.6 cm/m^2 (45 mm) and LV FS <0.32 predicted poor outcome.
Crawford et al 1990 (408)	prospective	MVR	48	survival, LV function	LV EF <0.50 predicted survival; ESV >50 mL/m^2 predicted persistent LV dilatation.
Reed et al 1991 (437)	prospective	MVR	176	survival	LA area >7.0 cm^2/m^2, end-systolic LV thickness/radius <0.4, and PAWP >9 mm Hg predicted poor survival.
Wisenbaugh et al 1994 (413)	registry	MVR MVR-CP	26 35	survival, LV function	ESD, EDD, and FS predicted poor survival and LV function; only ESD significant in multivariate analysis.
Enriquez-Sarano et al 1994 (412)	retrospective	MVR repair	214 195	survival	LV EF ≤0.60 predicted poor survival whether MVR or CP was performed; EF estimated by echo FS or visual analysis.
Enriquez-Sarano et al 1994 (436)	retrospective	MVR repair	104 162	LV function	EF, ESD, LV diameter/thickness ratio, and end-systolic wall stress predicted outcome; EF estimated by echo FS or visual analysis

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

improvement, and postoperative LV function are summarized in Table 20. The timing of surgery for asymptomatic patients was controversial, but most would now agree that mitral valve surgery is indicated with the appearance of echocardiographic indicators of LV dysfunction. These include LV ejection fraction ≤0.60 and/or LV end-systolic dimension ≥45 mm (Figure 6). 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 (412), although repair is clearly preferred. Although some recommend a slightly lower threshold ejection fraction (0.55), it must be emphasized that, unlike timing of AVR for AR, LV ejection fraction should not be allowed to fall into the lower limit of the normal range in patients with chronic MR (412,433–435). The data regarding postoperative survival are much stronger with LV ejection fraction than end-systolic dimension (408,411,412), whereas both ejection fraction and end-systolic dimension strongly influence postoperative LV function and heart failure (405,406,408,413,436). Outcome is also influenced by LV wall thickness–to–radius ratio (436,437).

Mitral valve surgery should also be recommended for symptomatic patients with evidence of LV systolic dysfunction (ejection fraction ≤0.60, end-systolic dimension ≥45 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 mitral valve repair appears likely, surgery should still be contemplated, provided ejection fraction is ≥0.30 (Figure 6). 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 (241).

d. Asymptomatic Patients With Normal Left Ventricular Function. As noted previously, repair of a severely regurgitant valve may be contemplated in an asymptomatic patient with normal LV function in order to preserve LV size and function and prevent the sequelae of chronic MR. Although there are no 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 (see below). This approach 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 episodic or chronic atrial fibrillation in whom there is a high likelihood of successful valve repair (see below).

e. Atrial Fibrillation. Atrial fibrillation is a common, potentially morbid arrhythmia associated with MR. Preoperative atrial fibrillation is an independent predictor of reduced long-term survival after mitral valve surgery for chronic MR (412). The persistence of atrial fibrillation after mitral valve surgery can lead to thromboembolism and partially nullifies an advantage of mitral repair by requiring anticoagulation. Predictors of the persistence of atrial fibrillation after successful valve surgery are the presence of atrial fibrillation for >1 year and left atrial size >50 mm (438). In one study, an even shorter duration of preoperative atrial fibrillation (3 months) was a predictor of persistent atrial fibrillation after mitral valve repair (439); persistent atrial fibrillation after surgery occurred in 80% of patients with preoperative atrial fibrillation ≥3 months but in no patient with preoperative atrial fibrillation <3 months. Although patients who develop atrial fibrillation also usually manifest other symptomatic or functional changes that

would warrant mitral valve repair or MVR, many clinicians would consider the onset of episodic or chronic atrial fibrillation to be an indication in and of itself for surgery (Figure 6) (432,439).

f. Feasibility of Repair Versus Replacement. As noted above, in many cases the type of operation, repair versus MVR, 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 mitral valve disease that caused MR. Nonrheumatic posterior leaflet prolapse due to degenerative mitral valve disease or a ruptured chordae tendineae can usually be repaired (440,441). Involvement of the anterior leaflet diminishes the likelihood of repair, and 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 and ischemic involvement of the mitral valve and calcification of the mitral valve leaflets or annulus diminish the likelihood of repair even in experienced hands.

Recommendations for Mitral Valve Surgery in Nonischemic Severe Mitral Regurgitation

Indication	*Class*
1. Acute symptomatic MR in which repair is likely.	I
2. Patients with NYHA functional Class II, III, or IV symptoms with normal LV function defined as ejection fraction >0.60 and end-systolic dimension <45 mm.	I
3. Symptomatic or asymptomatic patients with mild LV dysfunction, ejection fraction 0.50 to 0.60, and end-systolic dimension 45 to 50 mm.	I
4. Symptomatic or asymptomatic patients with moderate LV dysfunction, ejection fraction 0.30 to 0.50, and/or end-systolic dimension 50 to 55 mm.	I
5. Asymptomatic patients with preserved LV function and atrial fibrillation.	IIa
6. Asymptomatic patients with preserved LV function and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise).	IIa
7. Asymptomatic patients with ejection fraction 0.50 to 0.60 and end-systolic dimension <45 mm and asymptomatic patients with ejection fraction >0.60 and end-systolic dimension 45 to 55 mm.	IIa
8. Patients with severe LV dysfunction (ejection fraction <0.30 and/or end-systolic dimension >55 mm) in whom chordal preservation is highly likely.	IIa
9. Asymptomatic patients with chronic MR with preserved LV function in whom mitral valve repair is highly likely.	IIb
10. Patients with MVP and preserved LV function who have recurrent ventricular arrhythmias despite medical therapy.	IIb
11. Asymptomatic patients with preserved LV function in whom significant doubt about the feasibility of repair exists.	III

5. Ischemic Mitral Regurgitation. The outlook for the patient with ischemic MR is substantially worse than that for regurgitation from other causes (402,442). A worse prognosis accrues from the fact that ischemic MR is usually caused by LV dysfunction resulting from myocardial infarction. Furthermore, the mitral valve itself is usually anatomically normal and MR is secondary to papillary muscle dysfunction and/or displacement that make repair of the valve more difficult. On the other hand, coronary artery bypass graft surgery may improve LV function and reduce ischemic MR. In many patients with transient severe MR due to ischemia, myocardial revascularization can eliminate episodes of severe MR.

In severe MR secondary to acute myocardial infarction, hypotension and pulmonary edema often occur. Treatment is aimed at hemodynamic stabilization, usually with insertion of an intra-aortic balloon pump. Occasionally, revascularization of the coronary artery supplying an ischemic papillary muscle can lead to improvement in mitral valve competence. However, such improvement is rare, and correction of acute severe ischemic MR usually requires valve surgery. Unlike nonischemic MR, in which mitral repair is clearly the operation of choice, the best operation for ischemic MR is controversial (443,444). In one recent report, MVR had a better outcome than repair, especially when annular dilatation rather than chordal or papillary muscle rupture was the cause of MR (444).

6. Evaluation of Patients After Mitral Valve Replacement or Repair. After mitral valve surgery, follow-up is necessary to detect late surgical failure and assess LV function, as discussed in detail in section VII.C.3. of these guidelines. 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.

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 >75, especially if MVR must be performed or if the patient has concomitant CAD (427). In such patients, the goal of therapy is to improve the quality of life rather than prolong it. Thus, surgery may be performed in asymptomatic younger patients to preserve LV function, but it is hard to argue this position in patients older than 75. For such patients, symptoms are an important guide in deciding whether or not surgery is necessary. Under most circumstances, asymptomatic patients or patients with mild symptoms should be treated medically.

F. Multiple Valve Disease

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) yield 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 based on understanding the potential derangements in hemodynamics and LV function and the probable benefit of medical

versus surgical therapy. The committee has developed no specific recommendations in this section.

2. Mixed Single-Valve Disease. *a. Pathophysiology.* In mixed mitral or aortic valve disease, one 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 where 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 requiring 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 (106), a high gradient in predominant regurgitation 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 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.

b. Diagnosis. (1) 2-D 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 and mitral valves 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 management of mixed valve disease. Mitral valve 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 is 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 (445). 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.

(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 including exercise hemodynamics may be important. For example, resting hemodynamics in mixed mitral disease might show a transmitral gradient of 5 mm Hg, a valve area of 1.5 cm^2, and 2+ MR with a resting pulmonary artery wedge pressure of 15 mm. However, with exercise, the wedge pressure may 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 (446).

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 (thermodilution, Fick, etc) 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–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 may be difficult in the very large and/or spherical left ventricles encountered in valvular regurgitation (447). In general, the utility of this approach is limited. Doppler pressure half-time may be very useful in this situation.

c. 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 AS-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. Combined Mitral Stenosis and Aortic Regurgitation. *a. 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 (248). 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 mitral valve 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.

b. Management. Mechanical correction of both lesions is eventually necessary in most patients. Development of symptoms or pulmonary hypertension is the usual indication for intervention.

When mechanical correction is anticipated in predominant MS, balloon mitral valvotomy followed by AVR obviates the need for double valve replacement, which has a higher risk of complications than single valve replacement. In most cases, it is advisable to perform mitral valvotomy first and then follow the patient for symptomatic improvement. If symptoms disappear, correction of AR can be delayed.

4. Combined Mitral Stenosis and Tricuspid Regurgitation. *a. 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 (448). 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 (449). On the other hand, if there is severe rheumatic deformity of the tricuspid valve, competence is likely to be restored only by surgery.

b. 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.

c. Management. If the mitral valve 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 (449).

If mitral valve surgery is performed, concomitant tricuspid annuloplasty should be considered, especially if there are preoperative signs or symptoms of right-heart failure, rather than risking severe persistent TR, which may necessitate a second operation (450). However, TR that seems severe on echocardiography but does not cause elevation of right atrial or right ventricular diastolic pressure will generally improve greatly after MVR. If intraoperative assessment suggests that TR is functional without significant dilatation of the tricuspid annulus, it may not be necessary to perform an annuloplasty.

5. Combined Mitral and Aortic Regurgitation. *a. 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, ie, 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.

b. Diagnosis. Doppler echocardiographic interrogation shows bivalve regurgitation and an enlarged left ventricle. 2-D echocardiography is usually performed to assess severity of AR and MR, LV size and function, left atrial size, pulmonary artery pressure, and feasibility of mitral valve repair.

6. Combined Mitral and Aortic Stenosis. *a. Pathophysiology.* Combined stenotic disease is almost always secondary to rheumatic heart disease. Obstruction of flow at the mitral valve diminishes aortic valve flow as well. Thus, the problem of evaluating aortic valve severity in a low flow–low gradient situation often exists.

b. 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 2-D and Doppler echocardiographic studies to evaluate 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 mitral valve is acceptable for balloon valvotomy, this should be attempted first. If mitral balloon valvotomy is successful, the aortic valve should then be reevaluated.

7. Combined Aortic Stenosis and Mitral Regurgitation. *a. 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 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.

b. Diagnosis and Therapy. Noninvasive evaluation should be performed with 2-D 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 mitral valve morphology in patients with these combined lesions. Patients with severe AS and severe MR (with abnormal mitral valve morphology) with symptoms, LV dysfunction, or pulmonary hypertension should undergo combined AVR and MVR or mitral valve repair. 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 mitral valve morphology. Intraoperative transesophageal echocardiography and, if necessary, visual inspection of the mitral valve should be performed at the time of AVR to determine whether additional mitral valve surgery is warranted in these patients.

In patients with mild to moderate AS and severe MR in whom surgery on the mitral valve 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 ≥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 2-D or transesophageal echocardiography as well as visual inspection by the surgeon may be important in determining the need for concomitant AVR.

G. Tricuspid Valve Disease

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 of right ventricular systolic and/or diastolic pressure, right ventricular cavity enlargement, and tricuspid annular dilatation (451,452); right ventricular systolic hypertension occurs in MS, pulmonic valve stenosis, and the various causes of pulmonary hypertension. Right ventricular diastolic hypertension occurs in dilated cardiomyopathy and right ventricular failure of any cause (451,452).

Abnormalities of the tricuspid valve leading to TR can occur with rheumatic valvulitis, infective endocarditis, carcinoid, rheumatoid arthritis, radiation therapy, trauma, Marfan syndrome, tricuspid valve prolapse, papillary muscle dysfunction, or congenital disorders such as Ebstein's anomaly (451) or a cleft tricuspid valve as part of atrioventricular canal malformations. Anorectic drugs may also cause TR, as indicated in section III.H. of these guidelines.

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 (453). 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.

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 (454). Because acute rheumatic fever 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 mitral valve.

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 (455), pulsatile varicose veins (456), or a venous systolic thrill and murmur in the neck (457). Other associated clinical features are related to the cause of TR.

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 (458), right ventricular 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 (18–22). This is not an indication for either routine follow-up or prophylaxis against bacterial endocarditis. Thus, clinical correlation and judgment must accompany the echocardiographic results. Systolic pulmonary artery pressures ≥55 mm Hg are likely to cause TR with anatomically normal tricuspid valves, whereas TR occurring with systolic pulmonary artery pressures <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 (452).

3. Management. The patient's clinical status and the etiology 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 right ventricular 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 2-D and Doppler echocardiography for preoperative diagnosis and assessment. Intraoperative transesophageal Doppler echocardiography allows refinement of annuloplasty techniques to optimize outcome (459–461). At present, surgery on the tricuspid valve for TR occurs commonly at the time of mitral valve surgery. However, there are no long-term data regarding the value of such an approach.

Tricuspid valve balloon valvotomy has been advocated for tricuspid stenosis of various etiologies (462–464). 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 (465). Tricuspid valve and chordal reconstruction can be attempted in some cases of TR resulting from endocarditis and trauma (466–468). In recent years, annuloplasty has become an established surgical approach to significant TR (469–473).

When the valve leaflets themselves are diseased, abnormal, or destroyed, valve replacement with a low-profile mechanical valve or bioprosthesis is often necessary (474). 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.

Recommendations for Surgery for Tricuspid Regurgitation

Indication	*Class*
1. Annuloplasty for severe TR and pulmonary hypertension in patients with mitral valve disease requiring mitral valve surgery.	**I**
2. Valve replacement for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair.	**IIa**
3. Valve replacement or annuloplasty for severe TR with mean pulmonary artery pressure <60 mm Hg when symptomatic.	**IIa**
4. Annuloplasty for mild TR in patients with pulmonary hypertension secondary to mitral valve disease requiring mitral valve surgery	**IIb**
5. Valve replacement or annuloplasty for TR with pulmonary artery systolic pressure <60 mm Hg in the presence of a normal mitral valve, in asymptomatic patients, or in symptomatic patients who have not received a trial of diuretic therapy.	**III**

H. Valvular Heart Disease Associated With Anorectic Drugs

In addition to the common causes of the valvular lesions described in the preceding sections, there are a number of uncommon causes of valvular heart disease related to systemic diseases, drugs, 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 etiologies. In general, the management strategies for patients with these disorders are directed toward management of the underlying disease process and diagnosis and management of the associated valvular disease according to the guidelines developed for each of the valvular lesions in sections III.A. through III.G.

However, it is appropriate to address the issue of valvular heart disease associated with anorectic agents because of the current widespread concern of patients and healthcare professionals that has developed since this association was reported in the summer of 1997. Investigators at the Mayo Clinic and the MeritCare Medical Center in Fargo, ND, reported 24 patients receiving the combination of fenfluramine and phentermine in whom unusual valve morphology and associated regurgitation were identified in both left-sided and right-sided heart valves (475); all had AR and/or MR, and 12 had TR. Eight patients had associated pulmonary hypertension. Five patients underwent valve replacement surgery, and the histopathological findings of the excised valves included plaque-like encasement of the leaflets and chordal structures with intact valve architecture. The echocardiographic and histopathological findings were similar to those described in patients with carcinoid or ergotamine-induced valvular heart disease (476–480). All 24 patients were symptomatic and had heart murmurs; thus, the frequency of valvular pathology in asymptomatic patients receiving the combination of fenfluramine-phentermine could not be determined. When this initial series was published, it was accompanied by a letter to the editor from the Food and Drug Administration (481) reporting additional cases of valvular heart disease in 28 patients taking the fenfluramine-phentermine combination, as well as a few patients taking a combination of dexfenfluramine and phentermine, fenfluramine alone, or dexfenfluramine alone. A left-sided heart valve was involved in all cases. A total of 85 single cases were reported to the FDA by August 1997. In addition, the FDA also reported 5 echocardiographic prevalence surveys (482) in which 86 of 271 patients (32%) receiving combination fenfluramine-phentermine for 6 to 24 months had evidence of significant AR and/or MR, as did 6 of 20 patients (30%) receiving dexfenfluramine with or without phentermine. The prevalence of valvular regurgitation was consistent among the 5 reporting centers (range, 29% to 36%).

In light of this information, the drugs fenfluramine and dexfenfluramine were withdrawn from the market in September 1997. However, a lower prevalence of valvular abnormalities was reported in a survey of 21 centers that performed echocardiography in a total of 746 patients (483); in this survey, 21 patients (8%) were reported to have valvular regurgitation with the same threshold definitions as in the FDA report.

The risk of valvular heart disease associated with exposure to fenfluramine or dexfenfluramine, alone or in combination with phentermine, has been addressed in 3 recent peer-reviewed studies, one of which was a case-control study (483a), one a population-based study (483b), and one a randomized, double-blind placebo-controlled clinical trial (483c). The prevalence of AR and/or MR in patients exposed to these drugs varied widely among the 3 studies (from as high as 26% to as low as <1%), related primarily to differences in patient selection and study design. The 2 studies which used Doppler echocardiography to detect valvular regurgitation (483a, 483c) differed considerably in terms of the prevalence of the valve lesions and its statistical significance in comparison to control groups, which may be related to differences in the anorectic agents and the duration of exposure. It does appear that the prevalence of significant valvular regurgitation may be related to the duration of exposure to the anorectic agents (483b, 483d) and that patients exposed for only brief periods of time have less risk of developing valvular regurgitation.

In addition to the uncertainties regarding the prevalence of

valvular disease in patients receiving combination- or single-drug therapy, the natural history of the valve disease during anorectic drug treatment and the natural history after drug withdrawal are unknown and await further clinical investigation. Thus, the risk of valvular heart disease relative to the benefit of weight reduction in patients with morbid obesity is unknown.

Considering these unknown variables and the rapidly evolving information linking fenfluramine and dexfenfluramine (with or without phentermine) to valvular heart disease, it is not possible to derive definitive diagnostic and treatment guidelines for patients who have received these anorectic drugs. Hence, clinical judgment is important. The US Department of Health and Human Services (DHHS), through the Centers for Disease Control and Prevention and the National Institutes of Health, published interim recommendations on November 14, 1997 (484,485). The DHHS recommended that,

1. All persons exposed to fenfluramine or dexfenfluramine for any period of time, either alone or in combination with other agents, should undergo a medical history and cardiovascular examination by their physicians to determine the presence or absence of cardiopulmonary signs or symptoms.
2. An echocardiography evaluation should be performed on all persons who were exposed to fenfluramine or dexfenfluramine for any period of time, either alone or in combination with other agents, and who exhibit cardiopulmonary signs (including a new murmur) or symptoms suggestive of valvular disease (eg, dyspnea).
3. Although the clinical importance of asymptomatic valvular regurgitation in exposed patients and the risk for developing bacterial endocarditis in these patients are unknown, practitioners should strongly consider performing echocardiography on all persons—regardless of whether they have cardiopulmonary signs or symptoms—who have been exposed to fenfluramine or dexfenfluramine for any period of time, either alone or in combination with other agents, BEFORE the patient undergoes any invasive procedure for which antimicrobial prophylaxis is recommended by the 1997 AHA guidelines. Any echocardiographic findings that meet the AHA criteria for prophylaxis—regardless of whether they are attributable to possible fenfluramine or dexfenfluramine use—should be recognized as indications for antibiotic prophylaxis. The invasive procedures include certain medical or dental procedures in which antibiotic prophylaxis is recommended as defined by the 1997 AHA guidelines. For emergency procedures for which cardiac evaluation cannot be performed, empirical antibiotic prophylaxis should be administered according to the 1997 AHA guidelines.
4. Because of the prevalence of minimal degrees of regurgitation in the general population, the current case definition of drug-associated valvulopathy should include exposed patients with echocardiographically demonstrated AR of mild or greater severity and/or MR of moderate or greater severity, based on published criteria (486,487).

The Committee on Management of Patients With Valvular Heart Disease adopted the majority of the DHHS recommendations. However, the committee recommends that certain DHHS statements remain open to interpretation by individual physicians because of the lack of conclusive scientific data for appropriate care of patients who have taken these drugs. Specifically, the committee interprets the DHHS statement that practitioners should "strongly consider" performing echocardiography on all persons before they undergo invasive procedures, such as dental procedures, regardless of whether signs or symptoms are present, as the need for the physician to consider the findings of a patient's cardiovascular physical examination and any other pertinent data before ordering the test.

All patients with a history of use of fenfluramine or dexfenfluramine should undergo a careful history and thorough cardiovascular physical examination. The physical examination should include auscultation with the patient in the upright position at end-expiration to detect AR and in the left lateral decubitus position to detect MR. 2-D and Doppler echocardiography should be performed in patients with symptoms, cardiac murmurs, or other signs of cardiac involvement (eg, widened pulse pressure or regurgitant cv waves in the jugular venous pulse). Patients whose body size prevents adequate cardiac auscultation should also undergo 2-D and Doppler echocardiography. For example, mild AR may be difficult to detect on auscultation in an obese patient. Patients with clinical and echocardiographic evidence of valvular heart disease should then undergo treatment and/or further testing according to the recommendations developed for the specific valve lesions addressed in the earlier sections of these guidelines. Modification of these recommendations may be necessary as more information on the natural history of these specific valve lesions becomes available.

In light of the current evidence, echocardiographic screening of all patients with a history of fenfluramine or dexfenfluramine use, especially asymptomatic patients without murmurs or associated findings, is not recommended. However, because of possible progression of subclinical valvular disease, asymptomatic patients without murmurs should undergo repeat physical examinations in 6 to 8 months.

Recommendations for Patients Who Have Used Anorectic Drugs*

Indication	*Class*
1. Discontinuation of the anorectic drug(s).	**I**
2. Cardiac physical examination.	**I**
3. Echocardiography in patients with symptoms, heart murmurs, or associated physical findings.	**I**
4. Doppler echocardiography in patients for whom cardiac auscultation cannot be performed adequately because of body habitus.	**I**

5. Repeat physical examination in 6 to 8 months for those without murmurs.	**IIa**
6. Echocardiography in all patients before dental procedures in the absence of symptoms, heart murmurs, or associated physical findings.	**IIb**
7. Echocardiography in all patients without heart murmurs.	**III**

***Fenfluramine or dexfenfluramine or the combination of fenfluramine-phentermine or dexfenfluramine-phentermine.**

IV. Evaluation and Management of Infective Endocarditis

Clinical suspicion of infective endocarditis may be raised by the presence of fever and other systemic symptoms coupled with physical findings such as Osler's nodes, petechiae, Janeway lesions, Roth spots, splenomegaly, and a cardiac murmur. At present, these physical signs are less commonly encountered, and definitive diagnosis is made by demonstrating an offending organism by blood culture. Three sets of blood cultures, obtained at intervals ≥1 hour within the first 24 hours, is the norm; however, in selected patients, 5 to 6 sets of blood cultures may be needed, and some patients have culture-negative endocarditis (see below). Additionally, echocardiography has provided an important tool for recognizing both valvular structural abnormality and vegetations. The yield for visualization of vegetations for transthoracic echocardiography is ≈60% to 77% and increases to ≈96% with transesophageal imaging. The latter technique usually provides better delineation of valvular anatomy and function. This is especially the case for evaluation of prosthetic valves (488). However, the absence of vegetations on echocardiography does not exclude the diagnosis of infective endocarditis, and the complete clinical condition should be considered.

Criteria for the diagnosis of infective endocarditis were proposed by Von Reyn and colleagues (489) with the results of blood cultures, clinical signs, and symptoms. Subsequently, the Duke criteria were developed to include evidence of endocardial involvement (490). Table 21 shows the modified Duke criteria by Bansal (27).

Table 21. Duke Criteria* for Clinical Diagnosis of Ineffective Endocarditis

- Major Criteria
  - Persistently positive blood cultures
    - Typical organisms for endocarditis: *Streptococcus viridans, S bovis,* "HACEK" group, community-acquired *Staphylococcus aureus* or enterococci in the absence of primary focus
    - Persistent bacteremia: ≥2 positive cultures separated by ≥12 h or ≥3 positive cultures ≥1 h apart or 70% blood culture samples positive if ≥4 are drawn
  - Evidence of endocardial involvement
    - Positive echocardiogram
      - Oscillating vegetation
      - Abscesses
      - Valve perforation
      - New partial dehiscence of prosthetic valve
    - New valvular regurgitation
- Minor Criteria
  - Predisposing heart condition
    - MVP, bicuspid aortic valve, rheumatic or congenital heart disease, intravenous drug abuse
  - Fever
  - Vascular phenomena
    - Major arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, Janeway lesions
  - Immunologic phenomena
    - Glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
  - Positive blood cultures: not meeting major criteria
  - Echocardiogram: positive but not meeting major criteria
- Diagnosis
  - 2 major criteria or
  - 1 major criterion plus 3 minor criteria or
  - 5 minor criteria

*From Bansal RC (27). Infective endocarditis. Med Clin North Am. 1995;79:1205–40. With permission. Modified from Durack DT, Lukes AS, Bright DK (490). New criteria for diagnosis of infective endocarditis. Am J Med. 1994;96:200–9. With permission.

A. Antimicrobial Therapy

Antimicrobial therapy in endocarditis is guided by identification of the causative organism. Eighty percent of cases of endocarditis are due to streptococci and staphylococci. The majority of native valve endocarditis is caused by *Streptococcus viridans* (50%) and *Staphylococcus aureus* (20%). The latter organism is also the most frequent organism in endocarditis resulting from intravenous drug abuse. Eighty percent of tricuspid valve infection is by *S 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 frequent offending organism. Late-onset prosthetic valve endocarditis follows the profile of native valve endocarditis: ie, streptococci *(viridans)* and staphylococci. *Enterococcus faecalis* and *Enterococcus faecium* account for 90% of enterococcal endocarditis, 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,* and *Kingella* species) have become important causes of endocarditis. They cause large vegetations (>1 cm), large-vessel emboli, 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. The AHA recommendations for antimicrobial regimens are given in Tables 22 through 27 (491).

Table 22. Native Valve Endocarditis Involving Penicillin-Susceptible *Streptococcus viridans* and *Streptococcus bovis* (Minimum Inhibitory Concentration ≤0.1 μg/mL)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium or	12–18 million U/24 h IV either continuously or in 6 equally divided doses	4	Preferred in most patients >65 y and those with impairment of the eighth nerve or renal function.
Ceftriaxone sodium	2 g once daily IV or IM†	4	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	When obtained 1 h after a 20–30 min IV infusion or IM injection, serum concentration of gentamicin of approximately 3 μg/mL is
With gentamicin sulfate‡	1 mg/kg IM or IV every 8 h	2	desirable; trough concentration should be <1 μg/mL.
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to β-lactams; peak serum concentrations of vancomycin should be obtained 1 h after completion of infusion and should be in the range of 30–45 μg/mL for twice-daily dosing.

Abbreviations: IV = intravenous; IM = intramuscular. *Dosages recommended are for patients with normal renal function. For nutritionally variant streptococci, see Table 24. †Patients should be informed that IM injection of ceftriaxone is painful. ‡Dosing of gentamicin on a mg/kg basis will produce higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. (Ideal body weight for men is 50 kg + 2.3 kg/in. >5 ft; ideal body weight for women is 45.5 kg + 2.3 kg/in. >5 ft.) Relative contraindications to use of gentamicin are age >65 y, renal impairment, or impairment of the eighth nerve. Other potentially nephrotoxic agents (eg, nosteroidal anti-inflammatory drugs) should be used cautiously in patients receiving gentamicin. §Vancomycin dosage should be reduced in patients with impaired renal function. Vancomycin given on a mg/kg basis will produce higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. Each dose of vancomycin should be infused over ≥1 h to reduce the risk of the histamine-release "red man" syndrome. From Wilson et al (491) with permission.

Table 23. Native Valve Endocarditis Involving *Streptococcus viridans* and *Streptococcus bovis* Relatively Resistant to Penicillin G (Minimum Inhibitory Concentration >0.1 μg/mL and <0.5 μg/mL)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	18 million U/24 h IV either continuously or in 6 equally divided doses	4	Cefazolin or other first-generation cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	2	the immediate type.
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to β-lactams.

Abbreviations: IV = intravenous; IM = intramuscular. *Dosages recommended are for patients with normal renal function. †For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 22 footnotes. ‡For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 22 footnotes. From Wilson et al (491) with permission.

Table 24. Standard Therapy for Endocarditis Due to Enterococci*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6	4-wk therapy recommended for patients with symptoms <3 mo in duration; 6-wk therapy recommended for pts with symptoms
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4–6	>3 mo in duration.
Ampicillin sodium	12 g/24 h IV either continuously or in 6 equally divided doses	4–6	
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4–6	
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6	Vancomycin therapy is recommended for patients allergic to β-lactams; cephalosporins are not acceptable alternatives for patients allergic to penicillin.
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4–6	

Abbreviations: IV = intravenous; IM = intramuscular. *All enterococci causing endocarditis must be tested for antimicrobial susceptibility to selected optimal therapy. This table is for endocarditis due to gentamicin- or vancomycin-susceptible enterococci, *Streptococci viridans* with a minimum inhibitory concentration of >0.5 μg/mL, nutritionally variant *S viridans*, or prosthetic valve endocarditis caused by *S viridans* or *Streptococcus bovis*. Antibiotic dosages are for patients with normal renal function. †For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 22 footnotes. ‡For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 22 footnotes. From Wilson et al (491) with permission.

Table 25. Endocarditis Due to Staphylococcus in the Absence of Prosthetic Material*

Antibiotic	Dosage and Route	Duration	Comments
Methicillin-susceptible staphylococci			
Regimens for non–β-lactam-allergic patients			
Nafcillin sodium or oxacillin sodium	2 g IV every 4 h	4–6 wk	Benefit of additional aminoglycosides has not been established.
With optional addition of gentamicin sulfate†	1 mg/kg IM or IV every 8 h	3–5 d	
Regimens for β-lactam-allergic patients Cefazolin (or other first-generation cephalosporins in equivalent dosages)	2 g IV every 8 h	4–6 wk	Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin.
With optimal addition of gentamicin†	1 mg/kg IM or IV every 8 h	3–5 d	
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6 wk	Recommended for patients allergic to penicillin.
Methicillin-resistant staphylococci			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6 wk	

Abbreviations: IV = intravenous, IM = intramuscular. *For treatment of endocarditis due to penicillin-susceptible staphylococci (minimum inhibitory concentration ≤0.1 μg/mL), aqueous crystalline penicillin G sodium (Table 22, first regimen) can be used for 4 to 6 wk instead of nafcillin or oxacillin. Shorter antibiotic courses have been effective in some drug addicts with right-sided endocarditis due to *Staphylococcus aureus*. †For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 22 footnotes. ‡For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 22 footnotes. From Wilson et al (491) with permission.

Table 26. Endocarditis Due to Staphylococcus in the Presence of a Prosthetic Valve or Other Prosthetic Material*

Antibiotic	Dosage and Route	Duration, wk	Comments
Regimen for methicillin-resistant staphylococci			
Vancomycin hydrochloride†	30 mg/kg per 24 h IV in 2 or 4 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	≥6	
With rifampin‡ and	300 mg orally every 8 h	≥6	Rifampin increases the amount of warfarin sodium
With gentamicin sulfate§‖	1.0 mg/kg IM or IV every 8 h	2	required for antithrombotic therapy.
Regimen for methicillin-susceptible staphylococci			
Nafcillin sodium or oxacillin sodium	2 g IV every 4 h	≥6	First-generation cephalosporins or vancomycin should be used in patients allergic to β-lactam.
With rifampin‡ and	300 mg orally every 8 h	≥6	Cephalosporins should be avoided in patients with
With gentamicin sulfate§‖	1.0 mg/kg IM or IV every 8 h	2	immediate-type hypersensitivity to penicillin or with methicillin-resistant staphylococci.

Abbreviations: IV = intravenous; IM = intramuscular. *Dosages recommended are for patients with normal renal function. †For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 22 footnotes. ‡Rifampin plays a unique role in the eradication of staphylococcal infection involving prosthetic material; combination therapy is essential to prevent rifampin resistance. §For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 22 footnotes. ‖Use during initial 2 wk. From Wilson et al (491) with permission.

Table 27. Therapy for Endocarditis Due to HACEK Microorganisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium Hominis*, *Eikenella corrodens*, and *Kingella kingae*)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Ceftriaxone sodium†	2 g once daily IV or IM†	4	Cefotaxime sodium or other third-generation cephalosporins may be substituted
Ampicillin sodium‡	12 g/24 h IV either continuously or in 6 equally divided doses	4	
With gentamicin sulfate§	1 mg/kg IM or IV every 8 h	4	

Abbreviations: IV = intravenous, IM = intramuscular. *Antibiotic dosages are for patients with normal renal function. †Patients should be informed that IM injection of ceftriaxone is painful. ‡Ampicillin should not be used if laboratory tests show β-lactamase production. §For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 22 footnotes. From Wilson et al (491) with permission.

B. Culture-Negative Endocarditis

Culture-negative endocarditis most frequently (62%) results from prior antibiotic treatment before blood cultures were drawn (493,494). The other reasons for negative blood cultures are infections due to *Candida; Aspergillus;* or fastidious, slow-growing organisms (492) and noninfective endocarditis such as Libman-Sacks endocarditis in patients with systemic lupus erythematosus. A proposed regimen for culture-negative, presumed bacterial endocarditis (492) is shown in Table 28.

C. Endocarditis in HIV-Seropositive Patients

Endocarditis in patients who are HIV-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 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 (491).

D. Indications for Echocardiography in Endocarditis

Echocardiography is useful for 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 (495). The indications for transthoracic and transesophageal echocardiography are discussed in the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2). Transesophageal imaging is more sensitive in detecting vegetations than transthoracic imaging (488,496). Echocardiography may be useful in the case of culture-negative endocarditis (497) or the diagnosis of a persistent bacteremia whose source remains unidentified after appropriate evaluation (2).

Table 28. Fungal Endocarditis and Culture-Negative Endocarditis*

Agent	Dosage and Route	Duration, wk
Fungal endocarditis*		
Amphotericin B with or without flucytosine	1 mg/kg per day IV (total dose 2.0–2.5 g)	6–8
	150 mg/kg per day PO in 4 divided doses	6–8
Culture-negative endocarditis†		
Vancomycin plus gentamicin	15 mg/kg IV every 12 h	6
	1 mg/kg IM or IV every 8 h	6

*Recommendations for fungal endocarditis were not part of the AHA recommendations on infective endocarditis (491). †Proposed regimen for culture-negative, presumed bacterial endocarditis (492).

Recommendations for Echocardiography in Infective Endocarditis: Native Valves

Indication	*Class*
1. Detection and characterization of valvular lesions, their hemodynamic severity, and/or ventricular compensation.*	I
2. Detection of vegetations and characterization of lesions in patients with congenital heart disease in whom infective endocarditis is suspected.	I
3. Detection of associated abnormalities (eg, abscesses, shunts).*	I
4. Reevaluation studies in complex endocarditis (eg, virulent organism, severe hemodynamic lesion, aortic valve involvement, persistent fever or bacteremia, clinical change, or symptomatic deterioration).	I
5. Evaluation of patients with high clinical suspicion of culture-negative endocarditis.*	I
6. Evaluation of bacteremia without a known source.*	IIa
7. Risk stratification in established endocarditis.*	IIa
8. Routine reevaluation in uncomplicated endocarditis during antibiotic therapy.	IIb
9. Evaluation of fever and nonpathological murmur without evidence of bacteremia.	III

***Transesophageal echocardiography may provide incremental value in addition to information obtained by transthoracic imaging. From the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2).**

Recommendations for Echocardiography in Infective Endocarditis: Prosthetic Valves

Indication	*Class*
1. Detection and characterization of valvular lesions, their hemodynamic severity, and/or ventricular compensation.*	I
2. Detection of associated abnormalities (eg, abscesses, shunts).*	I
3. Reevaluation in complex endocarditis (eg, virulent organism, severe hemodynamic lesion, aortic valve involvement, persistent fever or bacteremia, clinical change, or symptomatic deterioration).	I
4. Evaluation of suspected endocarditis and negative cultures.*	I
5. Evaluation of bacteremia without a known source.*	I
6. Evaluation of persistent fever without evidence of bacteremia or new murmur.*	IIa
7. Routine reevaluation in uncomplicated endocarditis during antibiotic therapy.*	IIb
8. Evaluation of transient fever without evidence of bacteremia or new murmur.	III

***Transesophageal echocardiography may provide incremental value in addition to that obtained by transthoracic imaging. From the ACC/AHA Guidelines for the Clinical Application of Echocardiography (2).**

E. 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 (491). Recent 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 (498,499). Monotherapy with ceftriaxone or combination therapy with an aminoglycoside has been tried as an outpatient therapeutic option (500). However, more data are needed to determine with

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

F. Indications for Surgery in Patients With Active 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 (442,501–525). 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. Early consultation with a cardiovascular surgeon is recommended as soon as the diagnosis of aortic or mitral valve endocarditis is made 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, those with infections resistant to antibiotic therapy, and those with fungal endocarditis. It is recognized that the presence of valvular vegetations poses a threat of embolic events. Echocardiography, especially with transesophageal imaging, identifies vegetations and provides size estimation in many instances. Patients with a vegetation diameter >10 mm have a significantly higher incidence of embolization than those with a vegetation diameter ≤10 mm (488), and this risk appears to be higher in patients with mitral valve endocarditis than aortic valve endocarditis. However, operation on the basis of vegetation size alone is controversial.

Patients with prosthetic valves receiving warfarin anticoagulation who develop endocarditis should have their warfarin discontinued and replaced with heparin. This recommendation is less related to the possibility of hemorrhagic complications of endocarditis (526) 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.

Recommendations for Surgery for Native Valve Endocarditis*

Indication	*Class*
1. Acute AR or MR with heart failure.	I
2. Acute AR with tachycardia and early closure of the mitral valve.	I
3. Fungal endocarditis.	I
4. Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm.	I
5. Evidence of valve dysfunction and persistent infection after a prolonged period (7 to 10 days) of appropriate antibiotic therapy, as indicated by presence of fever, leukocytosis, and bacteremia, provided there are no noncardiac causes for infection.	I
6. Recurrent emboli after appropriate antibiotic therapy.	IIa
7. Infection with gram-negative organisms or organisms with a poor response to antibiotics in patients with evidence of valve dysfunction.	IIa
8. Mobile vegetations >10 mm.	IIb
9. Early infections of the mitral valve that can likely be repaired.	III
10. Persistent pyrexia and leukocytosis with negative blood cultures.	III

*Criteria also apply to repaired mitral and aortic allograft or autograft valves. Endocarditis defined by clinical criteria with or without laboratory verification; there must be evidence that function of a cardiac valve is impaired.

Recommendations for Surgery for Prosthetic Valve Endocarditis*

Indication	*Class*
1. Early prosthetic valve endocarditis (first 2 months or less after surgery).	I
2. Heart failure with prosthetic valve dysfunction.	I
3. Fungal endocarditis.	I
4. Staphylococcal endocarditis not responding to antibiotic therapy.	I
5. Evidence of paravalvular leak, annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new-onset conduction disturbances.	I
6. Infection with gram-negative organisms or organisms with a poor response to antibiotics.	I
7. Persistent bacteremia after a prolonged course (7 to 10 days) of appropriate antibiotic therapy without noncardiac causes for bacteremia.	IIa
8. Recurrent peripheral embolus despite therapy.	IIa
9. Vegetation of any size on or near the prosthesis.	IIb

*Criteria exclude repaired mitral valves or aortic allograft or autograft valves. Endocarditis is defined by clinical criteria with or without laboratory verification.

V. Management of Valvular Disease in Pregnancy

A. 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, leading to hypotension with weakness and lightheadedness. These symptoms resolve quickly with a change in position (527).

Table 29. 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 >75% of systemic pressures)
6. Aortic and/or mitral valve disease with severe LV dysfunction (EF <0.40)
7. Mechanical prosthetic valve requiring anticoagulation
8. AR in Marfan syndrome

Abbreviations: EF = ejection fraction.

Table 30. Valvular Heart Lesions Associated With Low Maternal and Fetal Risk During Pregnancy

1. Asymptomatic AS with low mean gradient (<50 mm Hg) in presence of normal LV systolic function (EF >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 and with normal LV systolic function
5. Mild to moderate MS (MVA >1.5 cm^2, gradient <5 mm Hg) without severe pulmonary hypertension
6. Mild to moderate pulmonary valve stenosis

Abbreviations: EF = ejection fraction, MVA = mitral valve area.

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 (527).

Pregnancy is also associated with a hypercoagulable state owing to relative decreases in protein S activity, stasis, and venous hypertension (528). Estrogens may interfere with collagen deposition within the media of the medium- and large-sized 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.

B. Physical Examination

The physical examination of the normal parturient is notable for a slightly fast resting heart rate, bounding pulses (although not truly water-hammer), a widened pulse pressure with a low normal peak systolic pressure, and warm extremities. Venous pressure is usually elevated above the normal range 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 heart sound is usually physiologically split but may also widen and appear fixed during the later stages of pregnancy. Third heart sounds are common. A soft grade 1 to 2 midsystolic murmur that is best heard along the mid to upper left sternal edge is a frequent finding (24). A continuous murmur, reflecting either a venous hum or a mammary soufflé, may sometimes be heard during careful 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 soufflé 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 (eg, MS, AS). On the other hand, murmurs of AR or MR may actually attenuate in the face of lowered systemic vascular resistance (529).

C. 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 (530). A large minority of women will demonstrate Doppler evidence of "physiological" MR in the absence of structural valve disease. Atrioventricular valve incompetence may derive 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.

D. General Management Guidelines

Clinical experience has shown that there are several cardiac conditions in which the physiological changes of pregnancy are poorly tolerated. Most experts would agree that, 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 29. Lesions associated with low risk during pregnancy are listed in Table 30.

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 obstetrical team accustomed to working with high-risk patients is encouraged. Drugs should generally be avoided whenever possible (Table 31).

E. Specific Lesions

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. The most common rheumatic lesion in this age group remains MS. Patients with mild to moderate MS can almost always be managed with judicious use of diuretics and β-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. β-blockers are chiefly indicated to treat or prevent tachycardia to optimize diastolic filling. Although the nonselective β-blocker propranolol has been in use for decades, some authorities recommend a cardioselective β-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.

For 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 and/or fetal complications, although caution is advised in interpreting outcomes from individual centers reporting relatively few patients (531–540). 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 (541).

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,

Table 31. Effects of Cardiovascular Drugs Taken During Pregnancy

Drug	Potential Fetal Adverse Effects	Safety
Warfarin	Crosses placental barrier, fetal hemorrhage in utero, embryopathy, central nervous system abnormalities	Unsafe
Heparin	None reported	Probably safe
Digoxin	Low birth weight	Safe
Quinidine	Toxic dose may induce premature labor and cause damage to fetal eighth cranial nerve	Safe
Procainamide	None reported	Safe
Disopyramide	May initiate uterine contractions	*
Lidocaine	High blood levels and fetal acidosis may cause central nervous system depression	Safe
Mexiletine	Fetal bradycardia, IUGR, low Apgar score, neonatal hypoglycemia, neonatal bradycardia, and neonatal hyperthyroidism	*
Flecainide	1 reported fetal death	*
Propafenone	None reported	*
Adenosine	None reported. Use during first trimester limited to a few patients.	Safe
Amiodarone	IUGR, prematurity, hypothyroidism	Unsafe
Calcium channel blocking agents	Fetal distress due to maternal hypotension	*
β-adrenergic blocking agents	IUGR, apnea at birth, bradycardia, hypoglycemia, hyperbilirubinemia; β_2-blockade blocking agents may initiate uterine contractions	Safe
Hydralazine	None reported	Safe
Sodium nitroprusside	Potential thiocyanate toxicity with high dose, fetal mortality with nitroprusside in animal studies	Potentially unsafe
Organic nitrates	Fetal heart rate deceleration and bradycardia	*
ACE inhibitors	Skull ossification defect, IUGR, premature deliveries, low birth weight, oligohydramnios, neonatal renal failure, anemia and death, limb contractures, patent ductus arteriosus	Unsafe
Diuretic agents	Impairment of uterine blood flow and danger of placental hypoperfusion, thrombocytopenia, jaundice hyponatremia, bradycardia	Potentially unsafe

Abbreviation: IUGR = intrauterine growth retardation. *To date, only limited information is available, and safety during pregnancy cannot be established. Adapted from Elkayam U (527). Pregnancy and cardiovascular disease. In: Braunwald E, ed. Heart Disease. A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, Pa: WB Saunders; 1997:1857, with permission. The guidelines committee added warfarin, heparin, and hydralazine to this list.

mitral valve 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. ACE inhibitors are considered unsafe because of their multiple adverse effects on fetal development. There is wide experience with hydralazine, an agent generally considered safe. When mitral valve 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.

3. Aortic Stenosis. The most common cause of AS in pregnant women is congenital bicuspid disease. Patients with mild to moderate obstruction and normal LV systolic function can usually be managed conservatively through the entire pregnancy. Patients with more severe obstruction (pressure gradient >50 mm Hg) or symptoms should be advised to delay conception until relief of AS can be obtained. For those rare women with severe AS whose disease is first appreciated during pregnancy, consideration may have to be given to either percutaneous aortic balloon valvotomy (542,543) or surgery (depending on the anatomic findings) before labor and delivery if heart failure has developed or syncope has occurred. 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 cystic medial necrosis, which may predispose to spontaneous aortic dissection, usually in the third trimester.

4. Aortic Regurgitation. Isolated AR, like MR, can usually be managed medically with a combination of diuretics and, if necessary, vasodilator therapy (544). Women with symptoms and/or signs of LV failure should be carefully 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 Class III or IV symptoms. Consideration regarding LV size or systolic function in less symptomatic patients should not apply.

5. Pulmonary Valve Stenosis. Pulmonary valve stenosis may 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.

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, although greater care may be necessary to protect against diuretic-induced hypoperfusion.

7. Marfan Syndrome. The Marfan syndrome is an inheritable disorder of connective tissue that 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 and/or rupture are the most feared cardiovascular complications associated with pregnancy (545,546). Dissection can occur at any point along the aorta but most commonly originates in the ascending portion. Enlargement of the aortic root to >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 who is contemplating pregnancy should have a screening transthoracic echocardiogram with careful assessment of aortic root dimensions. Enlargement ≥5.0 cm is considered an indication for elective repair before conception, usually with a composite valve-graft conduit and reimplantation of the coronary arteries. If aortic root enlargement (>4.0 cm) is first detected during pregnancy, some authorities recommend termination with prompt aortic repair, especially if serial echocardiographic 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. Obstetrical 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 β-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 (547). Finally, it should be pointed out that patients with Marfan syndrome and no identifiable cardiovascular abnormalities on examination or echocardiographic study can be safely shepherded through pregnancy and a normal vaginal delivery.

F. Endocarditis Prophylaxis

The Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association 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 (36). Many practitioners routinely provide antibiotics.

G. 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 (548–550). 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 (551,552). Surgery should be pursued only in the setting of medically refractory 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 (553). 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 (554).

H. Anticoagulation

Pregnant patients with mechanical valve prostheses have an obligate need for anticoagulation. Unfortunately, there remain significant problems and an impressive risk to both the mother and fetus of either hemorrhage or thrombosis with the use of either warfarin or heparin. For example, maternal thromboembolic phenomena may complicate from 4% to 14% of pregnancies in women with mechanical prostheses despite adequate anticoagulation as measured by the serum INR or aPTT (555,556).

Guidelines for the management of the pregnant patient with a mechanical prosthesis have been difficult to formulate due to the lack of adequate prospective randomized controlled trial data. Practice patterns vary widely and no consensus exists, as might be expected from the disparate results and claims of the retrospective and selective case series that have been reported to date. Appropriately designed trials are needed.

1. Warfarin. Warfarin crosses the placenta and has been associated with an increased incidence of spontaneous abortion, prematurity, and stillbirth. The manufacturer considers its use during pregnancy to be strictly contraindicated by virtue of its association with fetal deformity (embryopathy) and central nervous system abnormalities. The true incidence of warfarin embryopathy has been difficult to ascertain from the reported case series and has ranged from <5% to 67% (556,557). An estimate of 4% to 10% seems reasonable, based on recent reports (558,559). Its risk may be dose related and appears to be highest if exposure occurs during the 6th to 12th week of gestation. Fetal cerebral hemorrhage can complicate labor and delivery, especially if forceps evacuation is necessary.

2. Heparin. Heparin does not cross the placenta and is generally considered safer (558,560). Its longer-term use, however, is complicated by sterile abscesses, osteoporosis (albeit with a small risk of fracture), thrombocytopenia, and bleeding. Although heparin was previously considered the preferred antithrombotic agent, numerous case series and patient registries attest to an unacceptable incidence of thromboembolic complications, including fatal valve thrombosis, in high-risk pregnant women managed with subcutaneous heparin (12% to 24%) (558,561–564). Criticisms have been levied against these studies 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.

The choice of anticoagulant must be carefully considered and should derive from a consideration of maternal preferences regarding the competing risks to the mother and to the fetus. For many women, a 4% to 10% risk of warfarin embryopathy is unacceptable. These women may be unwilling to take warfarin at any time during the first trimester or throughout the entire pregnancy. Implicit in their choice of heparin, however, is the acceptance of increased risk of maternal hemorrhage or prosthetic valve thrombosis. Certainly, a full discussion of these issues is indicated before conception. The hazards of anticoagulation are considered by many to be so odious as to argue that mechanical prosthetic valves are relatively contraindicated in women of child-bearing potential.

Recommendations for Anticoagulation During Pregnancy in Patients With Mechanical Prosthetic Valves: Weeks 1 Through 35

Indication	*Class*
1. The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.*	I
2. High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose *not* to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the midinterval (6 hours after dosing) aPTT to 2 to 3 times control. Transition to warfarin can occur thereafter.	I
3. In patients receiving warfarin, INR should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.	IIa
4. Women at low risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted-dose subcutaneous heparin (17,500 to 20,000 U BID) to prolong the mid-interval (6 hours after dosing) aPTT to 2 to 3 times control.	IIb

*From the European Society of Cardiology Guidelines for Prevention of Thromboembolic Events in Valvular Heart Disease (304).

Recommendations for Anticoagulation During Pregnancy in Patients With Mechanical Prosthetic Valves: After the 36th Week

Indication	*Class*
1. Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.	IIa
2. If labor begins during treatment with warfarin, a caesarian section should be performed.	IIa
3. In the absence of significant bleeding, heparin can be resumed 4 to 6 hours after delivery and warfarin begun orally.	IIa

Low-molecular-weight heparins offer several potential advantages over unfractionated heparin, including greater bioavailability, ease of administration, lack of need for laboratory monitoring, and a lower incidence of thrombocytopenia and osteoporosis. They do not cross the placenta. Although they have been used 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 (563). The recommendation to add low-dose aspirin to a regimen of warfarin or intravenous or adjusted-dose subcutaneous heparin is based on an extrapolation of the results of a single randomized controlled trial of antithrombotic therapy in high-risk patients with prosthetic heart valves (564). 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 (560).

VI. Management of Valvular Heart Disease in Adolescents and Young Adults

Although the majority of valvular heart disease in older adults is acquired, the predominant etiology is congenital in children, adolescents, and young adults. It has been estimated that the prevalence of congenital heart disease is ≈440,000 in the United States (exclusive of bicuspid aortic valves; see below) (565). Many patients with congenital heart disease have some valvular involvement. Frequently, it is part of a more complex congenital cardiac anomaly, ie, tricuspid stenosis in children with pulmonary atresia and an intact ventricular septum or AS from aortic valve atresia as part of a hypoplastic left-heart 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 where it is the primary anatomic abnormality.

In evaluating valvular stenosis in children, the severity of valvular obstruction is usually reported as peak-to-peak systolic gradient at cardiac catheterization or maximum instantaneous gradient by Doppler 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-vessel pressure gradients for semilunar valves and mean pressure gradients for atrioventricular valves the reference standards. With the development of Doppler echocardiographic assessment of valvular obstruction, most pediatric cardiologists have continued to rely on gradients calculated from peak velocity using the formula gradient=4V2 for the semilunar valves and mean gradients for the atrioventricular valves rather than on valve area. The peak gradient measured by Doppler velocity (based on maximum instantaneous velocity) is higher than the peak-to-peak gradient measured at catheterization. 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 children, 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 (566).

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.

A. Aortic Stenosis

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

Much of what has been written in these guidelines for adults with acquired AS may be transferred to the adolescent or young adult. However, certain important differences must be emphasized. Throughout childhood, the aortic annulus and aortic valve must grow 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 may 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 (567) 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 >12 years of age showed very small increases. Those with higher initial gradients had a greater likelihood of demonstrating an increase in the gradient.

Recently, long-term results of the original cohort have been reported (568), with a mean follow-up period of 20 years. Only 20% of those with initial peak LV–to–peak aortic pressure gradients <25 mm Hg at initial catheterization had any intervention. However, in those with an initial peak gradient >50 mm Hg, arrhythmias, sudden death, and other morbid events (including endocarditis, congestive heart failure, syn-

cope, angina, myocardial infarction, stroke, and pacemaker insertion) occurred at a rate of ≈1.2% per year. Sudden cardiac death occurred in 25 of the 370 patients followed over ≈8,000 patient years, an 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.

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.

Recommendations for Diagnostic Evaluation of the Adolescent or Young Adult With Aortic Stenosis*

Indication	*Class*
1. ECG.*	I
2. Echo-Doppler study.*	I
3. Graded exercise test.†	IIa
4. Cardiac catheterization† for evaluation of gradient.	IIa
5. Chest x-ray.*	IIb
6. Coronary arteriography in the absence of history suggestive of concomitant CAD.	III

*Yearly if echo-Doppler gradient >36 mm Hg (velocity ≥3 m/s). Every 2 years if echo-Doppler gradient <36 mm Hg (peak velocity <3 m/s). †If echo-Doppler gradient >36 mm Hg (velocity >3 m/s) and patient interested in athletic participation or if clinical findings and echo-Doppler are disparate.

Balloon valvotomy for calcific AS in older adults has been at best very short-term palliation. In contrast, the results of balloon valvotomy in children and adolescents with obstruction due to fusion of commissures have been considerably more efficacious. 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% (569). In a single-institution study of 148 patients dilated at age 1 month to 20 years (570), midterm results showed an 8-year actuarial survival of 95%, with 3 of the 4 deaths occurring in infants who were dilated at <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 is incomplete because balloon valvotomy was introduced in the 1980s.

Although balloon dilation has become standard in children and adolescents with AS, it is rarely recommended in older adults because even short-term palliation is uncommon. 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 their early 20s, although some older young adults without heavily calcified valves may also benefit.

Because balloon valvotomy has resulted in good long-term palliation with little morbidity and little or no short- or intermediate-term mortality in children, adolescents, and young adults in their early 20s, the indications for intervention are considerably more liberal than those in older adults in whom intervention usually involves valve replacement. Although data are not yet available, reducing the gradient is likely to reduce the small incidence of sudden unexpected death (usually while exercising) (571) as well as the extent of interstitial myocardial fibrosis, which has been observed in children and adolescents who died and had evidence of repolarization abnormalities on ECG.

Children and young adults with Doppler gradients of 70 to 80 mm Hg or more (peak velocity >4.2 m/s), those who develop LV repolarization or ischemic changes on the ECG (T-wave inversion or ST depression) at rest or with exercise, and those with symptoms may be considered for cardiac catheterization and possible balloon dilation. The gradient should be confirmed hemodynamically before proceeding with dilation, and it is reasonable to perform valvotomy in patients with catheterization gradients >60 mm Hg. Patients with less severe gradients (50 to 70 mm Hg by Doppler echocardiography) who are interested in participating in vigorous athletics or those contemplating pregnancy are also commonly referred for balloon dilation. Surgical valvotomy has now been replaced in most centers by balloon valvotomy but is a reasonable alternative if skilled interventional cardiologists are not available.

Recommendations for Aortic Balloon Valvotomy in the Adolescent or Young Adult (≤21) With Normal Cardiac Output*

Indication	*Class*
1. Symptoms of angina, syncope, and dyspnea on exertion, with catheterization peak gradient ≥50 mm Hg.†	I
2. Catheterization peak gradient >60 mm Hg.	I
3. New-onset ischemic or repolarization changes on ECG at rest or with exercise (ST depression, T-wave inversion over left precordium) with a gradient >50 mm Hg).†	I
4. Catheterization peak gradient >50 mm Hg if patient wants to play competitive sports or desires to become pregnant.	IIa
5. Catheterization gradient <50 mm Hg without symptoms or ECG changes.	III

*Adolescents and young adults almost invariably have normal or increased cardiac output. If cardiac index <2 L/min/m^2, lower gradients should be used. †If gradient <50 mm Hg, other causes of symptoms should be explored.

When balloon aortic valvotomy is ineffective or significant AR is present, valve replacement may be necessary. Because bioprostheses have reduced durability in the young, mechanical valves have been commonly used. The long-term cumulative risks of endocarditis, thromboembolism, and bleeding from anticoagulation over a 20- to 40-year time frame have been problematic. Recently, the approach of replacing the aortic valve with a pulmonary autograft by means of a pulmonary or aortic homograft to replace the native pulmonary valve, as first performed by Ross, has gained acceptance in some centers (115,572–575). Preliminary results indicate low surgical risk, with the majority of autografts performing well for at least a decade. This approach has the advantage of not requiring anticoagulation, an important issue for active adolescents and younger adults, including women contemplating pregnancy.

B. Aortic Regurgitation

AR is an uncommon isolated congenital lesion, although it may occasionally be found in adolescents and young adults with a bicuspid aortic valve, discrete subaortic obstruction, or prolapse of one 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. The indications for surgery with isolated AR or mixed aortic valve disease are at present similar to adults, that is, symptoms, LV dysfunction (ejection fraction <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 right ventricular outflow tract is substantiated in long-term studies, the indications for autograft valve replacement are likely to become more liberal.

Recommendations for Aortic Valve Surgery (Replacement With Mechanical Valve, Homograft, or Pulmonary Autograft) in the Adolescent or Young Adult With Chronic Aortic Regurgitation

Indication	*Class*
1. Onset of symptoms.	I
2. Asymptomatic patients with LV systolic dysfunction (ejection fraction <0.50) on serial studies 1 to 3 months apart.	I
3. Asymptomatic patients with progressive LV enlargement (end-diastolic dimension >4 SD above normal).	I
4. Moderate AS (gradient >40 mm Hg) (peak-to-peak gradient at cardiac catheterization).	IIb
5. Onset of ischemic or repolarization abnormalities (ST depression, T-wave inversion) over left precordium at rest.	IIb

C. Mitral Regurgitation

Isolated congenital MR is an extremely uncommon cardiac condition. MR can be associated with MVP in adolescents or young adults with connective tissue, metabolic, or storage diseases. MR can be seen with acquired inflammatory diseases such as rheumatic fever, endocarditis, or Kawasaki disease or with certain collagen vascular disorders.

The most common cause of MR in children is atrioventricular septal defects. This is a defect 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 possible. The most common long-term sequela of surgery is MR, which may 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 III.E.). When associated with congestive heart failure or deteriorating LV systolic function on echocardiography or angiography, surgery should be performed. In children with atrioventricular septal defects, MR can usually be reduced or eliminated with surgery. In the postoperative atrioventricular septal defect or MR secondary to MVP, rheumatic fever, or inflammatory disease, it is frequently possible to decrease the regurgitation with mitral annuloplasty. Occasionally, MVR with a mechanical or biological valve is necessary. When valve repair rather than replacement is likely, surgery for severe MR may be contemplated in the absence of heart failure or LV dysfunction.

Recommendations for Mitral Valve Surgery in the Adolescent or Young Adult With Congenital Mitral Regurgitation With Severe MR

Indication	*Class*
1. NYHA functional Class III or IV symptoms.	I
2. Asymptomatic patients with LV systolic dysfunction (ejection fraction ≤0.60).	I
3. NYHA functional Class II symptoms with preserved LV systolic function if valve repair rather than replacement is likely.	IIa
4. Asymptomatic patients with preserved LV systolic function in whom valve replacement is highly likely.	IIb

D. Mitral Stenosis

In developed countries, virtually all MS in adolescents and young adults is 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, resulting 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 (576). 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 left ventricle 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 coarctation of the aorta.

The clinical, electrocardiographic, and radiologic features of congenital MS are similar to acquired MS in adults. The echocardiogram is beneficial in evaluating the mitral valve 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 older children, adolescents, and young adults, a transesophageal echocardiogram is sometimes necessary.

Medical management is of limited utility in these patients, but it is important to prevent and treat common complica-

tions such as pulmonary infections, endocarditis, and atrial fibrillation. Surgical intervention may be necessary in severe cases.

Recommendations for Mitral Valve Surgery in the Adolescent or Young Adult With Congenital Mitral Stenosis

Indication	*Class*
1. Symptomatic patients (NYHA functional Class III or IV) and mean mitral valve gradient >10 mm Hg on Doppler echocardiography.	I
2. Mildly symptomatic patients (NYHA functional Class II) and mean mitral valve gradient >10 mm Hg on Doppler echocardiographic study.	IIa
3. Systolic pulmonary artery pressure 50 to 60 mm Hg with a mean mitral valve gradient ≥10 mm Hg.	IIa
4. New-onset atrial fibrillation or multiple systemic emboli while receiving adequate anticoagulation.	IIb

The surgical management of congenital MS has improved considerably with the improved appreciation of the mechanism of mitral valve function and the improved ability to visualize the valve afforded by transesophageal echocardiography. In those with a parachute mitral valve, creation of fenestrations among the fused chordae may increase effective orifice area and improve symptoms dramatically. MVR 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 (577), but its utility is unproved. 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.

E. Tricuspid Valve Disease

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 children 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 right ventricular 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 variation in the severity of valve leaflet abnormalities. Some children may have severe TR, especially in the perinatal period, when pulmonary vascular resistance and resulting right ventricular 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 ≈25%.

Patients with Ebstein's anomaly may be asymptomatic with no cyanosis and no atrial arrhythmias. More commonly, they are cyanotic due to right-to-left shunting, which is associated with exercise intolerance. Right ventricular dysfunction may eventually lead to right-sided congestive heart failure frequently exacerbated by an atrial arrhythmia such as atrial tachycardia, atrial flutter, or atrial fibrillation.

Recommendations for Diagnostic Evaluation* of Ebstein's Anomaly of the Tricuspid Valve in the Adolescent or Young Adult

Indication	*Class*
1. ECG.	I
2. Chest x-ray.	I
3. Echo-Doppler study.	I
4. Pulse oximetry at rest and/or during exercise.	IIa
5. Electrophysiological study if documented or suspected atrial arrhythmia.	IIa

*Initial evaluation and every 1 to 3 years, depending upon severity.

The natural history of Ebstein's anomaly varies. In patients who present in the perinatal period, the 10-year actuarial survival is 61% (578). In a study that included more children who presented after the perinatal period, the probability of survival was 50% at 47 years of age (579). Predictors of poor outcome were NYHA functional Class III or IV symptoms, cardiothoracic ratio >65%, or atrial fibrillation. However, patients with Ebstein's anomaly who reach late adolescence and adulthood often have an excellent outcome (579).

Surgical management of Ebstein's anomaly remains challenging. For older children, adolescents, and young adults, tricuspid valve repair has been attempted. Reconstruction of the valve is occasionally 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.

Occasionally, the tricuspid valve is not reparable, and valve replacement with a bioprosthesis or a mechanical valve may be necessary. When present, atrial communications should be closed. If an accessory pathway is present, this should be mapped and obliterated either preoperatively in the electrophysiology laboratory or at the time of surgery.

Recommendations for Surgery in the Adolescent or Young Adult With Ebstein's Anomaly With Severe Tricuspid Regurgitation

Indication	*Class*
1. Congestive heart failure.	I
2. Deteriorating exercise capacity (NYHA functional Class III or IV).	I
3. Progressive cyanosis with arterial saturation <80% at rest or with exercise.	I
4. Progressive cardiac enlargement with cardiothoracic ratio >60%.	IIa
5. Systemic emboli despite adequate anticoagulation.	IIa
6. NYHA functional Class II symptoms with valve probably reparable.	IIa
7. Atrial fibrillation.	IIa
8. Deteriorating exercise tolerance (NYHA functional Class II).	IIa
9. Asymptomatic patients with increasing heart size.	IIb
10. Asymptomatic patients with stable heart size.	III

F. Pulmonic Stenosis

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, which project superiorly into the main pulmonary artery. Occasionally, the valve may be thickened and dysplastic, with the stenosis caused by inability of the valve leaflets to move sufficiently during ventricular systole (580).

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 light-headedness may rarely be seen, but sudden death is very unusual. Eventually, in the neonate or adult with long-standing untreated severe obstruction, TR and right ventricular failure may occur.

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

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

Recommendations for Initial Diagnostic Workup of Pulmonic Stenosis

	Severity of Pulmonic Stenosis	
Indication	*Mild* Class*	*Moderate-Severe† Class*
1. ECG.	I	I
2. Echo-Doppler study (transthoracic).	I	I
3. Chest x-ray.	IIa	IIa
4. Diagnostic cardiac catheterization.	III	IIb‡

***Right ventricular to pulmonary artery maximum instantaneous gradient <30 mm Hg by Doppler echocardiography. †Right ventricular to pulmonary artery gradient ≥30 mm Hg by Doppler echocardiography. ‡If catheterization gradient ≥50 mm Hg, balloon valvuloplasty should be performed (see recommendations for intervention).**

3. Clinical Course. The clinical course of children and young adults with pulmonary valve stenosis has been well described. The Natural History of Congenital Heart Defects study (581) in the mid 1960s and early 1970s followed 564 patients with valvular pulmonary stenosis with cardiac catheterization at 4- and 8-year intervals. On admission to the study, ≈15% were <2 years old; 20%, 12 to 21 years old; and the remainder, 2 to 11 years old. At initial cardiac catheterization, they were divided into 4 groups based on severity:<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 ≥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 <2 years old and/or those with initial gradients >40 mm Hg. Those not in either category had only a 4% chance of an increase in the gradient >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 >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 (582) reported on a 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. Less than 20% of patients managed medically during the first Natural History Study subsequently required a valvotomy, and only 4% of the operated patients 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 <25 mm Hg in the first Natural History Study, 96% were free of cardiac operation over a 25-year period.

Infective endocarditis was uncommon. Only 1 case developed in the 592 patients followed a median of 18 years, an incidence of 0.94 per 10,000 patient years. Although endocarditis prophylaxis has been recommended for patients with PS, the incidence and severity of infection are such that the morbidity from anaphylactic reactions to endocarditis prophylaxis may be as problematic as the disease itself.

Recommendations for Intervention in the Adolescent or Young Adult With Pulmonic Stenosis (Balloon Valvotomy or Surgery)

Indication	*Class*
1. Patients with exertional dyspnea, angina, syncope, or presyncope.	I
2. Asymptomatic patients with normal cardiac output (estimated clinically or determined by catheterization).	
a. Right ventricular to pulmonary artery peak gradient >50 mm Hg	I
b. Right ventricular to pulmonary artery peak gradient 40 to 49 mm Hg	IIa
c. Right ventricular to pulmonary artery peak gradient 30 to 39 mm Hg	IIb
d. Right ventricular to pulmonary artery peak gradient <30 mm Hg	III

Surgical relief of severe obstruction by valvotomy with a transventricular (583) or transpulmonary (584) artery approach predates the introduction of cardiopulmonary bypass. A nonsurgical approach with balloon valvotomy was described in 1982 (585) and by the late 1980s had become the procedure of choice for the typically domed, thickened valve virtually everywhere in the United States, both for children (586) and adults (587,588). Surgery is still 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) (589) suggest results similar to surgical valvotomy, that is, little or no recurrence over a 22- to 30-year period.

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 β-blockade, but there is insufficient information to determine whether this is effective or necessary.

From the Natural History Study data, it would appear 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 severe, and infrequently follow up those with mild disease (590).

Recommendations for Follow-up Exams in Pulmonic Stenosis

	Severity of Pulmonic Stenosis	
Indication	*Mild* Class*	*Moderate to Severe† Class*
1. ECG.	I	I
2. Echo Doppler.	I	I
3. Chest x-ray.	IIb	IIa
4. Catheterization (for evaluation of gradient).	III	III

***<29 mm Hg gradient; testing every 5 to 10 years. †>30 mm Hg gradient; testing every 3 years (consideration should be given to balloon or surgical valvuloplasty).**

G. Pulmonary Regurgitation

Pulmonary valve regurgitation is an uncommon congenital lesion seen occasionally with what has been described as idiopathic dilation of the pulmonary artery. In this condition, the annulus of the pulmonary valve dilates, causing the leaflets to fail 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, 87% had pulmonary regurgitation by Doppler echocardiography in the second Natural History Study, although it was audible in only 58%. The echocardiogram tended to overestimate severity when 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 right ventricular systolic dysfunction was uncommon; it was 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 operated on in the late 1950s and 1960s continue to do well for up to 35 years after surgery (591). However, a small group with long-standing pulmonary regurgitation has developed a very dilated right ventricle and diminished right ventricular 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. Pulmonary valve replacement, usually with a homograft, has been attempted, but follow-up data are too preliminary to develop recommendations at this time.

VII. Management of Patients With Prosthetic Heart Valves

A. Classification of Prosthetic Heart Valves

Heart valve prostheses consist of an orifice, through which blood flows, and an occluding mechanism that closes and opens the orifice. There are 2 classes of heart valve: mechanical prostheses, with rigid, manufactured occluders, and biological or tissue valves, with flexible leaflet occluders of animal or human origin. A list of FDA-approved prosthetic heart valves is given in Table 32.

1. Mechanical Valves. *a. Ball Valves.* The first successful valve replacement devices used a ball-in-cage design (592,593). Of these, only the Starr-Edwards valve has endured; it has been used more than 200,000 times. The ball is a silicone

rubber polymer impregnated with barium sulfate for radiopacity that oscillates in a cage of cobalt chromium alloy.

b. Disk Valves. Tilting disk valves use a circular disk as an occluder, which is retained by wirelike arms or closed loops that project into the orifice. The disks are graphite with a coating of pyrolytic carbon, and the housings are stainless steel or titanium. The first successful low-profile design was the standard Björk-Shiley tilting disk valve, introduced in 1969 (594). Approximately 360,000 standard valves were implanted. In the United States, Björk-Shiley models have been discontinued but are mentioned because many patients with standard or subsequently modified Björk-Shiley valves are still alive. The Medtronic Hall valve has a titanium housing and a carbon-coated disk with a unique central hole. The disk is retained and guided by a guide strut that protrudes through this hole. It has been used clinically since 1977.

c. Bileaflet Valves. Current development of mechanical valves is based on the bileaflet design, introduced by St. Jude Medical in 1977 and used >600,000 times. Unlike the free-floating occluders in ball and disk valves, the 2 semicircular leaflets of a bileaflet valve are connected to the orifice housing by a butterfly hinge mechanism. The leaflets swing apart during opening, creating 3 flow areas, 1 central and 2 peripheral.

2. Biological Valves. There is a wide variety of biological valves. The autograft valve refers to a translocation within the same individual, eg, of the pulmonary valve into the aortic valve position. The autologous (or autogenous) tissue valve involves fabricating a valve from the patient's own nonvalvular tissue, eg, pericardium. The homograft (or allograft) valve refers to transplantation from a donor of the same species; eg, a donor's aortic or pulmonary valve into a recipient's aortic or pulmonary position. The heterograft (or xenograft) valve is a transplant from another species, either an intact valve, eg, a porcine aortic valve, or a valve fashioned from heterologous tissue, eg, bovine pericardium.

The goal of biological valves is to reduce the complications associated with thromboembolism and the need for anticoagulation and in the aortic position to optimize hemodynamics.

a. Autograft Valves. The pulmonary autograft procedure consists of an autotransplant of the pulmonary valve to the aortic position; the pulmonary valve is then replaced by an aortic or pulmonary homograft or a heterograft. First described in 1967 (572), this operation is called the Ross procedure. Favorable long-term results have been reported (115,573–575). This procedure involves a double valve replacement with attendant early and late risks. However, late problems are likely to be related to the pulmonary valve prosthesis, which is easier to remedy but may require a second operation. The Ross procedure does not require FDA approval for clinical use; if a heterograft valve is used in the pulmonary position, it needs to be an FDA-approved device.

b. Autologous Pericardial Valves. This new category of prosthetic valve is an innovative attempt to combine the reproducibility and ease of insertion of a commercial stented heterograft valve with the benefits of autologous tissue. It is a frame-mounted autologous pericardial valve assembled from a kit in the operating room.

Table 32. FDA-Approved Prosthetic Heart Valves

Type	Manufacturer	Model	Year of First Clinical Use	Implants* (thousands)
Mechanical				
Ball	Baxter Edwards	Starr-Edwards	1965	200
Disk	Medtronic	Medtronic Hall	1977	178
	Medical Inc.	Omniscience	1978	48
	Alliance	Monostrut	1982	94
Bileaflet	St. Jude	St. Jude	1977	580
	Baxter Edwards	Duromedics	1982†	20
	CarboMedics	CarboMedics	1986	110
Biological				
Porcine	Medtronic	Hancock Standard	1970	177
		Hancock MO	1978	32
	Baxter Edwards	CE Standard	1971	400
		CE SupraAnnular	1982	45
	St. Jude	Toronto Stentless (TSP)	1991	5
	Medtronic	Free Style Stentless	1992	5
Pericardial	Baxter Edwards	CE	1982	35
Homograft	noncommercial‡		1962	12?
	Cryolife‡		1984	14
Autologous	noncommercial‡	Pulmonary autograft	1967	2?

Abbreviations: MO = modified orifice, CE = Carpentier-Edwards. *Approximate number of implants through part or all of 1994. †Discontinued in 1988. ‡Does not require FDA approval for clinical use. Adapted from Grunkemeier G, Starr A, Rahimtoola SH (616). Replacement of heart valves. In: O'Rourke RA, ed. The Heart: Update I. New York, NY: McGraw-Hill Publishing Co; 1996:98–123.

c. Homograft (or Allograft) Valves. Homograft valves were first used in the early 1960s (595,596). Three techniques of homograft AVR are used: (1) replacing only the valve in the subcoronary position; (2) complete aortic root replacement with reimplantation of the coronary arteries; and (3) miniroot replacement with the donor valve and attached aortic wall inserted within the host aorta below the coronary ostia. The homograft does not require FDA approval for clinical use.

The homograft valve is considered by many a preferable substitute for AVR in younger patients, especially those in whom anticoagulation is undesirable. It achieves excellent hemodynamics and has low thrombogenicity, and there is no need for anticoagulation. The drawbacks are a more technically demanding operation and low availability; however, the latter has been alleviated by commercial availability.

d. Porcine Heterograft (or Xenograft) Valves. Glutaraldehyde sterilizes valve tissue, renders it bioacceptable by destroying antigenicity, and stabilizes the collagen crosslinks for durability. The term bioprosthesis is used for a nonviable tissue of biological origin such as the Hancock and Carpentier-Edwards porcine valves (597).

Most porcine valves are mounted on rigid or flexible stents to which the leaflets and sewing ring are attached. However,

unstented versions have also been devised by several manufacturers and have been approved by the FDA for clinical use. Their goal is to achieve some of the potential benefit of a homograft valve, especially hemodynamics and perhaps durability, with an easily available commercial product. As with homografts, there are potentially 3 ways of implanting a stentless porcine valve (valve only, aortic root, miniroot). The standard porcine bioprosthesis is inserted into the annulus. The Carpentier-Edwards SupraAnnular Valve is implanted above the aortic annulus but sutured to it.

e. Bovine Pericardial Valves. Pericardial valves are tailored and sewn into a valvular configuration on a stented frame, with bovine pericardium as a fabric. This produces a valve that opens more completely than a porcine valve for better hemodynamics. Greater durability is also expected because there is extra tissue to allow for shrinkage and a higher percentage of collagen to be cross-linked during fixation. The Ionescu-Shiley, the first commercially available pericardial valve, experienced a higher failure rate than porcine valves and was taken off the market after ≈10 years. However, the failures were partly due to aspects of the design rather than an intrinsic problem with pericardial tissue itself.

The Carpentier-Edwards Pericardial Bioprosthesis is constructed without stitches passing through the leaflets that are present in the Ionescu-Shiley pericardial valve. Instead, the leaflets are anchored behind the stent pillars.

B. Complications of Prosthetic Heart Valves

1. Guidelines for Reporting Clinical Results. The analytic aspects of reporting clinical results of heart valves have evolved consistently since the first successful implants in 1960. Near the end of the first decade, as late (posthospital) experience accumulated, the need to analyze time-related events resulted in the introduction of actuarial analysis (598), which had been used for some time to analyze the results of cancer therapy (599). Later the use of linearized (constant hazard) rates (600,601), Cox regression (602), and multivariable parametric models (603) was advocated. However, the effectiveness of these refined statistical methods in comparing results from different series was limited by the lack of standardization in definitions and follow-up methods.

a. AATS/STS Guidelines for Clinical Reporting. In 1988, standards for defining and reporting complications 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 (AATS) and the Society of Thoracic Surgeons (STS) (604). These guidelines were revised in 1996 (605,606). The complications determined to be of critical importance in the 1996 guidelines are summarized as follows:

1. *Structural valvular deterioration* refers to any change in function of an operated valve resulting from an intrinsic abnormality causing stenosis or regurgitation.
2. *Nonstructural dysfunction* is a composite category that includes any abnormality resulting in stenosis or regurgitation of the operated valve that is not intrinsic to the valve itself exclusive of thrombosis and infection. This includes inappropriate sizing, also called valve prosthesis–patient mismatch (607).
3. *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.
4. *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.
5. *Bleeding event* (formerly anticoagulant hemorrhage) is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (eg, vision loss) or requires transfusion. The complication bleeding event applies to all patients, whether or not they are taking anticoagulants or antiplatelet drugs.
6. *Operated valvular endocarditis* is any infection involving 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 morbid events include reoperation; valve-related mortality; sudden unexpected, unexplained death; cardiac death; total deaths; and permanent valve-related impairment (605,606). In addition, valve prosthesis may produce hemolysis due either to the valve itself or associated perivalvular leak.

2. Valve-Related Complications. There is a wide range in the reported incidence of complications with the same prosthetic valve and between different valves (608). This is most likely due to variation among series rather than to valve type and model (609). It has been emphasized (610) that these include factors associated with patients (eg, ventricular function, comorbidities), medical center (eg, surgical variables, definitions of complications, thoroughness of follow-up), and data analysis (eg, influences of patient-related factors) (609). In addition, published data represent only a small fraction of valves implanted (610).

Many types of bias affect reported results (611), which might be overcome with randomized trials. However, randomized trials also have difficulties (612,613). 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.

a. Major Randomized Trials. The 2 major randomized clinical trials that have been reported are the Edinburgh Heart Valve Trial (121) and the Veterans Affairs Cooperative Study

on Valvular Heart Disease (124). Both studies compared mechanical valves with porcine bioprostheses.

The Edinburgh trial (121) compared the Björk-Shiley standard valve with porcine valves (initially the Hancock and later the Carpentier-Edwards) and reported actuarial comparisons at 5 and 12 years for 211 aortic and 261 mitral valve patients. Survival was better, but not significantly so, with the mechanical valve than the porcine valve (72% versus 52%, P = 0.08); this was somewhat offset by the increased risk of bleeding events. However, survival without reoperation was better with mechanical than bioprosthetic valves for MVR (74% versus 42%, P = 0.04) and AVR (75% versus 55%, P = 0.052).

The VA Study (124) compared the standard Björk-Shiley valve with the Hancock porcine valve in 575 men. The Hancock modified-orifice valve was used for sizes 21 to 23 mm in the aortic position, and the Hancock standard valve was used for all other sizes. Table 33 contains actuarial comparisons of the end point variables at 11 years. The risk for all valve-related complications is higher for mechanical valves during the first 5 years, but the cumulative risks converge by ≈10 years. At 11 years, the rates of both mortality and all valve-related complications were similar with mechanical and porcine valves, but the types of complication differed between the two; bleeding rates were higher with mechanical valves, and structural valve deterioration (and reoperation) rates were higher with bioprostheses.

Comparison of the actuarial event rates between these 2 trials (124) showed that bleeding and thromboembolism rates were higher in the VA study and reoperation rates were higher in the Edinburgh study. These differences could be partially accounted for by the composition of the 2 patient populations: patients in the Edinburgh trial were younger and received less anticoagulation, and this trial included women, double valve replacements, and a higher percentage of porcine valves in the mitral position.

Late long-term results show better survival in patients with mechanical valves compared with those with bioprostheses (particularly those in younger age groups). In the Edinburgh trial (121), 12-year survival was 42% versus 24% (P < 0.05) in patients with mechanical and porcine valves, respectively, in the mitral position, probably because of the high rate of bioprosthetic degeneration. In the VA trial (614), 15-year survival was 34% versus 23% (P = 0.02) in patients with mechanical and porcine valves, respectively, in the aortic position.

Nonrandomized studies in patients ≥65 years of age show a lower rate of structural valvular deterioration with the pericardial valve than with a porcine bioprosthesis (615).

C. Management of Patients With Prosthetic Heart Valves

1. Antibiotic Prophylaxis. *a. Infective Endocarditis.* All patients with prosthetic valves need appropriate antibiotics for prophylaxis against infective endocarditis (section II.B.).

b. Recurrence of Rheumatic Carditis. Patients with rheumatic heart disease continue to need antibiotics as prophylaxis against recurrence of rheumatic carditis (section II.B.).

2. Antithrombotic Therapy. All patients with mechanical valves require warfarin therapy, as indicated in Table 34 (617). Even with the use of warfarin, risk of thromboemboli is 1% to 2% per year (119,121,124,618), but the risk is considerably higher without treatment with warfarin (619). The risk of a clinical thromboembolism is ≈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 on warfarin therapy (119,121,124,620). Almost all studies have shown that risk of embolism is greater with a valve in the mitral position (mechanical or biological) than with one in the aortic position (121,608,619,621). 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 (620), before the valve is fully endothelialized.

a. Mechanical Valves. All patients with mechanical valves require warfarin. For mechanical prostheses in the aortic position, the INR should be maintained between 2.0 and 3.0

Table 33. Probability of Death Due to Any Cause, Any Valve-Related Complications, and Individual Valve-Related Complications 11 Years After Randomization

	Aortic Valve			Mitral Valve		
Event	Mechanical (n = 198)	Porcine (n = 196)	P	Mechanical (n = 88)	Porcine (n = 93)	P
Death from any cause	53 ± 4	59 ± 4	0.26	64 ± 5	67 ± 5	0.41
Any valve-related complications	62 ± 4	64 ± 4	0.64	71 ± 5	79 ± 6	0.34
Systemic embolism	16 ± 4	15 ± 3	0.49	18 ± 5	15 ± 4	0.61
Bleeding	43 ± 4	24 ± 4	< 0.001	41 ± 6	28 ± 7	0.02
Endocarditis	7 ± 2	8 ± 2	0.79	11 ± 4	17 ± 5	0.37
Valve thrombosis	2 ± 1	1 ± 1	0.33	1 ± 1	1 ± 1	0.95
Perivalvular regurgitation	4 ± 2	2 ± 1	0.28	17 ± 5	9 ± 6	0.05
Reoperation	7 ± 2	16 ± 4	0.07	21 ± 5	47 ± 9	0.23
Structural valve failure	0 ± 0	15 ± 4	< 0.001	0 ± 0	36 ± 8	< 0.001

Values are actuarial percentages ± standard error. Note: P values are for differences between mechanical and porcine valves; P < 0.001. Data from Hammermeister et al (124) as summarized in Grunkemeier et al (616) with permission.

Table 34. Antithrombotic Therapy: Prosthetic Heart Valves

	Warfarin (INR 2–3)	Warfarin (INR 2.5–3.5)	Aspirin (80–100 mg)
Mechanical Prosthetic Valves			
A. First 3 months after replacement		+	+
B. After first 3 months			
1. Aortic valve†	+		+
2. Aortic valve + "risk factor"*		+	+
3. Mitral valve		+	+
4. Mitral valve + "risk factor"*		+	+
Biological Prosthetic Valves			
A. First 3 months after replacement		+	+
B. After first 3 months			
1. Aortic valve			+
2. Aortic valve + "risk factor"*	+		+
3. Mitral valve			+
4. Mitral valve + "risk factor"*		+	+

Note: Depending on patient's clinical status, antithrombotic therapy must be individualized (see special situations in text). *Risk factors: Atrial fibrillation, LV dysfunction, previous thromboembolism, and hypercoagulable condition. †INR should be maintained between 2.5 and 3.5 for aortic disk valves and Starr-Edwards valves. Reprinted with permission from McAnulty JH, Rahimtoola SH (617). Antithrombotic therapy in valvular heart disease. In: Schlant R, Alexander RW, eds. *Hurst's The Heart, Arteries, and Veins*. 9th ed. New York, NY: McGraw-Hill Publishing Co; 1998:1867–74.

for bileaflet valves and Medtronic Hall valves and between 2.5 and 3.5 for other disk 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 (121,124,608,621–630). There was a difference of opinion regarding the Starr-Edwards valve in the aortic position, with a minority opinion to maintain the INR 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 (121,608,619, 621,624,625,629,630) and the greater risk of bleeding at higher INRs (625). In patients with aortic mechanical prostheses 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 (631). Some valves are thought to be more thrombogenic than others (particularly the tilting disk valves), and a case could be made for increasing the INR to between 3 and 4.5; however, this is associated with a considerably increased risk of bleeding (621,632).

The addition of low-dose aspirin (80 to 100 mg/d) to warfarin therapy (INR 2.0 to 3.5) not only further decreases the risk of thromboembolism (564,625,633–637) 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 (635,638). The risk of gastrointestinal irritation and hemorrhage with aspirin is dose dependent over the range of 100 to 1000 mg/d, and the antiplatelet effects are independent of dose over this range (639,640). There are no data in patients with prosthetic heart valves receiving warfarin and aspirin in doses of 100 to 325 mg/d. Doses of 500 to 1000 mg/d clearly increase the risk of bleeding (641–643). The addition of aspirin (80 to 100 mg/d) to warfarin should be strongly considered unless there is a contraindication to the use of aspirin (ie, bleeding or aspirin intolerance). This combination is particularly appropriate in patients who have had an embolus while on warfarin therapy, those with known vascular disease, and/or those who are known to be particularly hypercoagulable. As an example, such combination therapy is recommended by a committee addressing antithrombotic therapy in women during pregnancy (560). Anticoagulation in pregnant patients is controversial and is discussed in section V.H. of these guidelines.

It is important to note that thromboembolic risk is increased early after insertion of the prosthetic valve. The use of heparin early after prosthetic valve replacement before warfarin achieves therapeutic levels is controversial. In some patients, achievement of therapeutic INR can be delayed several days postoperatively because of mitigating complications.

b. 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 usually recommended (620), although in several centers only aspirin is used for biological valves in the aortic position. The risk is particularly high in the first few days after surgery and heparin should be started as soon as the risk of increased surgical bleeding is reduced (usually within 24 to 48 hours), with maintenance of PTT between 55 and 70 seconds. After an overlap of heparin and warfarin for 3 to 5 days, heparin 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 (121,124,620,644). 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 <0.30) (631).

Recommendations for Antithrombotic Therapy in Patients With Prosthetic Heart Valves

Indication		*Class*
1. First 3 months after valve replacement:	**Warfarin, INR 2.5 to 3.5**	**I**
2. ≥3 months after valve replacement:		
A. Mechanical valve		
AVR and no risk factor*		
Bileaflet valve or Medtronic Hall valve	**Warfarin, INR 2 to 3**	**I**
Other disk valves or Starr-Edwards valve	**Warfarin, INR 2.5 to 3.5**	**I**
AVR + risk factor*	**Warfarin INR 2.5 to 3.5**	**I**
MVR	**Warfarin INR 2.5 to 3.5**	**I**

B. Bioprosthesis		
AVR and no risk factor*	**Aspirin, 80 to 100 mg/d**	**I**
AVR and risk factor*	**Warfarin, INR 2 to 3**	**I**
MVR and no risk factor*	**Aspirin, 80 to 100 mg/d**	**I**
MVR and risk factor*	**Warfarin, INR 2.5 to 3.5**	**I**
3. Addition of aspirin, 80 to 100 mg once daily if not on aspirin.		**IIa**
4. Warfarin, INR 3.5 to 4.5 in high-risk patients when aspirin cannot be used.		**IIa**
5. Warfarin, INR 2.0 to 3.0 in patients with Starr-Edwards AVR and no risk factor.		**IIb**
6. Mechanical valve, no warfarin therapy.		**III**
7. Mechanical valve, aspirin therapy only.		**III**
8. Bioprosthesis, no warfarin and no aspirin therapy.		**III**

***Risk factors: Atrial fibrillation, LV dysfunction, previous thromboembolism, and hypercoagulable condition.**

c. Difficulties in Maintaining Anticoagulant Therapy. It is frequently difficult to maintain a patient at a fixed or relatively fixed level of anticoagulation due to changes in absorption of medication, the effects of various foods and medications, and changes in liver function. Therefore, in clinical practice, the patient 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.

d. Embolic Events During Adequate Antithrombotic Therapy. In the patient who has a definite embolic episode(s) while on adequate antithrombotic therapy, the dosage of antithrombotic therapy should be increased as follows:

- Warfarin, INR 2 to 3: 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 on aspirin: aspirin 80 to 100 mg/d should be initiated.
- Warfarin plus aspirin 80 to 100 mg/d: aspirin dose may also need to be increased to 325 mg/d 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/d and/or warfarin added to achieve INR of 2 to 3.

e. Excessive Anticoagulation. In most patients with INR above the therapeutic range, excessive anticoagulation can be managed by withholding warfarin and following the level of anticoagulation with serial INR determinations. Excessive anticoagulation (INR>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 managed by withholding warfarin and administering 2.5 mg of oral vitamin K_1 (phytonadione) (645). INR should be determined after 24 hours and subsequently as needed. Warfarin therapy is restarted and dose adjusted appropriately to ensure that INR is in the therapeutic range. In emergency situations, the use of fresh frozen plasma is preferable to high-dose vitamin K_1, especially parenteral vitamin K_1, because use of the latter increases the risk of overcorrection to a hypercoagulable state.

f. Antithrombotic Therapy in Patients Requiring Noncardiac Surgery/Dental Care. 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 (eg, a patient with a mechanical prosthesis with previous thromboemboli), the risk of a thromboembolus off warfarin could be 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 (646), but it is not clear that this increases the clinical risk of thromboembolism (647). In addition, when reinstituting warfarin therapy, there are theoretic 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, as indicated in Table 35 (617). 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 altering 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.

For most patients on warfarin, the drug should be stopped before the procedure so that the INR is $\leq$1.5 (which is often 48 to 72 hours after warfarin is discontinued) (617,648) and restarted within 24 hours after a procedure. Admission to the hospital or a delay in discharge to give heparin is usually unnecessary (633,647,649–651). Determining which patients are at very high risk of thrombosis and require heparin until warfarin can be reinstated may be difficult, and clinical judgment is required. Heparin can usually be reserved for those who have had a recent thrombosis or embolus (arbitrarily within 1 year), those with demonstrated thrombotic problems when previously off therapy, those with the Björk-Shiley valve (652–654), and those with $\geq$3 "risk factors." Such risk factors include atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis; many would also include LV dysfunction (ejection fraction <0.30) as a risk factor. A lower threshold for recommending heparin should be considered in patients with mechanical valves in the mitral position, in whom a single risk factor would be sufficient

Table 35. Antithrombotic Therapy in Patients Requiring Noncardiac Surgery/Dental Care

Usual Approach	
If patient on warfarin	· Stop 72 h before procedure · Restart in the afternoon on the day of procedure or after control of active bleeding
If patient on aspirin	· Stop 1 wk before procedure · Restart the day after procedure or after control of active bleeding
Unusual Circumstances	
1. Very high risk of thrombosis if off warfarin*	· Stop warfarin 72 h before procedure · Start heparin when INR falls below 2.0† · Stop heparin 6 h before procedure · Restart heparin within 24 h of procedure and continue until warfarin can be restarted and INR ≥2.0
2. Surgery complicated by postoperative bleeding	· Start heparin as soon after surgery as deemed safe and maintain PTT at 55–70 s until warfarin restarted and INR ≥2.0.
3. Very low risk from bleeding‡	· Continue antithrombotic therapy

*Clinical judgment: consider this approach if recent thromboembolus, Björk-Shiley valve, or 3 "risk factors" are present. Risk factors are atrial fibrillation, LV dysfunction, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis. One risk factor is sufficient to consider heparin in patients with mechanical valves in mitral position. †Heparin can be given in outpatient setting before and after surgery. ‡Eg, local skin surgery, teeth cleaning, and treatment for caries. From McAnulty JH, Rahimtoola SH (617). Antithrombotic therapy in valvular heart disease. In: Schlant R, Alexander RW, eds. *Hurst's The Heart, Arteries, and Veins*. 9th ed. New York, NY: McGraw-Hill Publishing Co; 1998:1867–1874. With permission.

evidence of high risk. When heparin is used, it should be started when INR falls below 2.0 (ie, 48 hours before surgery) and stopped 4 to 6 hours before the procedure. Heparin should be restarted as early after surgery as bleeding stability allows, and the aPPT should be maintained at 55 to 70 seconds until warfarin is restarted. After an overlap of 3 to 5 days, heparin may be discontinued when the desired INR is achieved. Home administration and management of heparin (and warfarin) can be arranged to minimize time in the hospital. Low-molecular-weight heparin is attractive because it is even more easily used outside the hospital; however, there are no data on patients with prosthetic heart valves (617), and low-molecular-weight heparin cannot be recommended at this time.

High-dose vitamin K_1 should not be given routinely, as this may create a hypercoagulable condition. For emergency situations, fresh frozen plasma is preferable to high-dose vitamin K_1.

g. Antithrombotic Therapy in Patients Needing Cardiac Catheterization/Angiography. Although some centers do not discontinue heparin before cardiac catheterization, most stop heparin 6 hours before the procedure and resume it 12 hours after the procedure. Under most circumstances, protamine should not be given. Antiplatelet therapy does not have to be stopped for these procedures.

In an emergent or semiemergent situation, cardiac catheterization can be performed in a patient taking warfarin, but preferably the drug should be stopped ≈72 hours before the procedure so that INR is ≤1.5 (see above). The drug should be restarted as soon as the procedure is completed. This is true for patients with biological valves receiving antithrombotic therapy as well as those with mechanical valves. If a patient has ≥1 risk factor(s) that predispose to thromboembolism, heparin should be started when INR falls below 2.0 and 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 off all antithrombotic therapy and INR should be ≤1.2; the same is also true if an LV puncture is to be performed (655). In patients who are to undergo transseptal or LV puncture and are receiving heparin therapy, heparin should be discontinued 4 to 6 hours before the procedure(s) and can be restarted without a bolus ≥4 hours after the sheath in the peripheral vessel has been removed.

h. Thrombosis of Prosthetic Heart Valves. Prosthetic valve obstruction 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. If the prosthesis is obstructed by pannus, thrombolytic therapy will be ineffective, and the valve needs to be replaced. Thrombolytic therapy for a prosthetic valve obstructed by thrombus is associated with significant risks and is often ineffective. Two recent extensive reviews (656,657) of thrombolytic therapy for left-sided prosthetic valve thrombosis reported that thrombolytic therapy is ineffective in 16% to 18% and acute mortality is 6%. The risk of thromboembolism is 12%; stroke, 3% to 10%; major bleeding episodes, 5%; nondisabling bleeding, 14%; and recurrent thrombosis, 11%. Patients who have a large clot, those with evidence of valve obstruction, and those in NYHA functional Classes III or IV because of prosthetic thrombosis should undergo early/immediate reoperation. Thrombolytic therapy in such patients is reserved for those in whom surgical intervention carries a high risk and those with contraindications to operation (656–659). Streptokinase and urokinase are the most frequently used thrombolytic agents. The duration of thrombolytic therapy depends on resolution of pressure gradients and valve areas to near-normal by Doppler echocardiography. Thrombolytic therapy should be stopped at 24 hours if there is no hemodynamic improvement or after 72 hours even if hemodynamic recovery is incomplete (656). If thrombolytic therapy is successful, it should be followed by intravenous heparin until warfarin achieves an INR of 3 to 4 for aortic prosthetic valves and 3.5 to 4.5 for mitral prosthetic valves. If partially successful, thrombolytic therapy may be followed by a combination of subcutaneous heparin twice daily (to achieve an aPTT of 55 to 80 seconds) plus warfarin (INR 2.5 to 3.5) for a 3-month period (656).

Patients with a "small clot" who are in NYHA functional

Class I or II and those with LV dysfunction should have in-hospital, short-term intravenous heparin therapy. If this is unsuccessful, they may receive a trial of continuous infusion thrombolytic therapy over several days. If this is unsuccessful or there is an increased risk associated with thrombolytic therapy, they may need reoperation. An alternative to thrombolytic therapy in patients who remain hemodynamically stable is to convert intravenous heparin to combined therapy with subcutaneous heparin (twice daily to an aPTT of 55 to 80 seconds) and warfarin (INR 2.5 to 3.5) for 1 to 3 months on an outpatient basis to allow for endogenous thrombolysis (656). If intravenous heparin, heparin/thrombolytic therapy, or heparin/warfarin is successful, warfarin doses should be increased so that INR is between 3.0 and 4.0 (around 3.5) for prosthetic aortic valves and between 3.5 and 4.5 (around 4.0) for prosthetic mitral valves. These patients should also receive low-dose aspirin.

3. Follow-up Visits. *a. 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, 2-D and Doppler echocardiography, complete blood count, BUN/creatinine, electrolytes, LDH, and INR, if indicated. The main focus of the examination is on signs that relate to functioning of the prosthesis or that might suggest the presence of infection or a myocardial infarction, conduction, or valvular disorder. Severe perivalvular mitral regurgitation may be inaudible on physical examination, a fact to remember when considering possible causes of functional deterioration in a patient.

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, left and right ventricular hypertrophy, left and right ventricular 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 and/or deterioration occur later.

Every prosthetic valve has an intrinsic degree of obstruction (607,660), and 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 have emerged for assessing 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. Phonocardiography can detect variant poppets if "normal" sounds were previously established but is rarely used in the 1990s. Radionuclide angiography 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.

b. 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 (661). The clinical course of patients with prosthetic heart valves is influenced by several factors (609), including ventricular 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 LDH. The frequency with which 2-D and Doppler echocardiography should be routinely performed in uncomplicated patients is uncertain, and there are no data on which to base this decision. The Committee on Management of Patients With Valvular Heart Disease did not reach consensus on this issue. The majority recommended no further echocardiographic testing 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 Guidelines for the Clinical Application of Echocardiography (2). However, a minority opinion recommended routine echocardiograms every year. The committee also failed to reach consensus on serial echocardiography in patients with bioprosthetic valves for whom there is an increasing risk of structural deterioration of the valve after 5 years in the mitral position and after 8 years in the aortic position. A minority opinion recommended annual echocardiography, whereas the majority recommended detailed histories and cardiac physical examinations with echocardiography when dictated by clinical circumstances such as a regurgitant murmur or change in symptoms. Once regurgitation is detected, close follow-up with 2-D and Doppler echocardiography every 3 to 6 months is indicated. The committee agreed that echocardiography is indicated in any patient with a prosthetic heart valve whenever there is evidence of a new murmur, there are questions about prosthetic valve integrity and function, or there are concerns about ventricular function.

Recommendations for Follow-up Strategy of Patients With Prosthetic Heart Valves

Indication	*Class*
1. History, physical exam, ECG, chest X-ray, echocardiogram, complete blood count, serum chemistries, and INR (if indicated) at first postoperative outpatient evaluation.*	I
2. Radionuclide angiography or magnetic resonance imaging to assess LV function if result of echocardiography is unsatisfactory.	I
3. Routine follow-up visits at yearly intervals with earlier reevaluations for change in clinical status.	I
4. Routine serial echocardiograms at time of annual follow-up visit in absence of change in clinical status.	IIb
5. Routine serial fluoroscopy.	III

*This evaluation should be performed 3 to 4 weeks after hospital discharge. In some settings, the outpatient echocardiogram may be difficult to obtain; if so, an inpatient echocardiogram may be obtained before hospital discharge.

c. Follow-up Visits in Patients With Complications. LV dysfunction and clinical heart failure after valve replacement may be the result of (1) preoperative LV dysfunction that persists or improves only partially; (2) perioperative myocardial damage; (3) other valve disease that has progressed; (4) complications of prosthetic heart valves; and (5) 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 2-D and Doppler echocardiography and, if necessary, transesophageal echocardiography and cardiac catheterization with angiography to determine the cause.

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, thrombosed prosthetic valves, and valve prosthesis–patient mismatch (607,660).

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.

D. Major Criteria for Valve Selection

In general, mitral valve repair is preferable to MVR, provided it is feasible and the appropriate skill and experience are available to perform the procedure successfully. Carefully selected patients with AR or AS in whom the valve is not calcified are also candidates for valve repair, with the same provisos as mitral valve repair and with the recognition that information regarding the early and late results of aortic valve repair for AR is quite limited at this time.

The major advantages of a mechanical valve are an extremely low rate of structural deterioration and a better survival rate in patients younger than 65 years after AVR, and for MVR in patients ≤50 years of age after MVR. The major disadvantages are the increased incidence of bleeding due to the need for antithrombotic therapy and the cost and disadvantages of antithrombotic therapy.

The major advantages of a bioprosthesis (whether porcine or pericardial) are a lower bleeding rate and lack of need for antithrombotic therapy. In addition, the rate of structural valve deterioration in patients ≥65 years is lower than in patients <65, especially in the aortic position (662–671). The influence of age on structural deterioration of porcine bioprosthetic valves is shown in Table 36. In patients ≥65 years undergoing AVR with a porcine bioprosthesis, the rate of structural deterioration is <10% at 10 years (663–665,668–671). The major disadvantage is the increased rate of structural valve deterioration and hence the need for reoperation in patients <65 years, particularly in those aged ≤50 years. Pericardial bioprostheses may have a lower rate of structural valve deterioration than porcine bioprostheses in patients ≥65 years (672,673).

Women who are contemplating pregnancy after valve replacement pose a difficult problem. The disadvantages of a mechanical valve are that the patient is at risk for complications of warfarin therapy that may affect the patient and/or fetus and for complications of heparin therapy (see section V.H. of these guidelines). It is likely that the risks may be lower in women who are compliant and have access to good medical care (674). If the patient needs warfarin therapy for another reason, then the anticoagulation required for a mechanical valve may not pose an additional risk. However, a mechanical valve may pose an additional risk if it requires a higher INR level than the underlying condition for which warfarin was initiated or if the initial indication for warfarin is not absolute. For example, for a patient in sinus rhythm with a previous history of atrial fibrillation and no previous history of systemic emboli, aspirin may be substituted for warfarin during pregnancy. In this situation, a mechanical valve would pose an additional risk. The disadvantage of a bioprosthesis is the relatively higher rate of early structural valve deterioration (553). As a result, reoperation for prosthetic valve replacement will likely be required with its attendant risks, including disability and death of young mothers. The Ross procedure (pulmonary autograft) or an aortic valve homograft is associated with a lower rate of such complications in young women and does not require anticoagulation. These procedures are strongly recommended for women who wish to become pregnant, provided that the

Table 36. Structural Valve Deterioration of Bioprosthetic Valves

Study, year	Mean follow-up, year	Number of valves		Time of SVD estimate, year	Age, year	Freedom from SVD (%)		Comments
		AVR	MVR			AVR	MVR	
Jamieson et al 1988 (663)	5.6	572	509	10	30–59	81 ± 4	78 ± 5	Carpentier-Edwards standard porcine bioprosthesis
					>60	91 ± 3	71 ± 9	
Cohn et al 1989 (664)	6.0	971	708	15	≤40	68 ± 9	68 ± 10	Hancock porcine bioprosthesis (includes 146 combined AVR + MVR procedures)
					41–69	86 ± 2	84 ± 13	
					≥70	94 ± 3	84 ± 10	
Jones et al 1990 (665)	8.3	610	528	10	<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	
Burr et al 1992 (668)	—	574	500	7	<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	100	100	
				13–15	<65	62 ± 8	37 ± 7	
					65–69	98 ± 3	63 ± 8	
					70–79	95 ± 5	74 ± 19	
					≥80	100	—	
Pelletier et al 1992 (669)	7.0	451	547	10	<45	70	55	Carpentier-Edwards standard (302 AVR, 324 MVR), improved annulus (97 AVR, 135 MVR), and 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	93	95	
Burdon et al 1992 (670)	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	
					>70	93 ± 3	62 ± 6	

Abbreviations: AVR = aortic valve replacement, MVR = mitral valve replacement, SVD = structural valve deterioration, TVR = tricuspid valve replacement.

necessary surgical skill and experience in performing these procedures are available. The options for prosthetic valves should be explained and discussed with younger women before valve replacement and pregnancy.

Pulmonary autograft and homograft valves have a very low rate of thromboemboli and possibly endocarditis. The long-term (20-year) incidence of structural valve deterioration is not certain. The autograft, if feasible to perform and if the appropriate skill and experience are available, is preferable in children because of the possibility of growth of the valve as the patient grows. These valves are available only for AVR.

If the patient needs antithrombotic therapy for any reason, for example, atrial fibrillation or presence of a mechanical valve in another position, then the major advantage of a biological valve is reduced substantially.

If the patient is small or has a small valve annulus that will not permit use of an adequately sized valve (≥23 mm for AVR, ≥31 mm for MVR), consideration should be given to aortic root/annular enlargement or use of an autograft/homograft in the aortic position. If a mechanical valve or bioprosthesis is used in such patients, then one with the best hemodynamic profile should be chosen.

Biological valves have a much higher rate of structural deterioration when implanted in patients with renal failure, those on hemodialysis, and those with hypercalcemia. Adolescent patients who are still growing have a high risk for accelerated biological valve calcification.

In patients undergoing repeat valve replacement, dysfunction of a biological valve may be a consideration for a mechanical valve, and a previously thrombosed mechanical valve is a consideration for a biological valve.

The above factors should be considered in choosing a prosthetic valve. Patients should be informed of the known risks and benefits of each device, and patient preferences and individual circumstances should be considered in deciding which prosthetic heart valve to use for each patient.

Recommendations for Valve Replacement With a Mechanical Prosthesis

Indication	*Class*
1. Patients with expected long life spans.	I
2. Patients with a mechanical prosthetic valve already in place in a different position than the valve to be replaced.	I
3. Patients in renal failure, on hemodialysis, or with hypercalcemia.	II
4. Patients requiring warfarin therapy because of risk factors* for thromboembolism.	IIa
5. Patients ≤65 years for AVR and ≤70 years for MVR.†	IIa
6. Valve rereplacement for thrombosed biological valve.	IIb
7. Patients who cannot or will not take warfarin therapy.	III

*Risk factors: atrial fibrillation, severe LV dysfunction, previous thromboembolism, and hypercoagulable condition. †The age at which patients may be considered for bioprosthetic valves is based on the major reduction in rate of structural valve deterioration after age 65 (662–671) and the increased risk of bleeding in this age group.

Recommendations for Valve Replacement With a Bioprosthesis

Indication	*Class*
1. Patients who cannot or will not take warfarin therapy.	I
2. Patients ≥65 years* needing AVR who do not have risk factors for thromboembolism.†	I
3. Patients considered to have possible compliance problems with warfarin therapy.	IIa
4. Patients >70 years* needing MVR who do not have risk factors for thromboembolism.†	IIa
5. Valve rereplacement for thrombosed mechanical valve.	IIb
6. Patients <65 years.*	IIb
7. Patients in renal failure, on hemodialysis, or with hypercalcemia.	III
8. Adolescent patients who are still growing.	III

*The age at which patients should be considered for bioprosthetic valves is based on the major reduction in rate of structural valve deterioration after age 65 (662–671) and increased risk of bleeding in this age group. †Risk factors: atrial fibrillation, severe LV dysfunction, previous thromboembolism, and hypercoagulable condition.

VIII. 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.

A. Probability of Coronary Artery Disease in Patients With Valvular Heart Disease

The probability of developing CAD in the general population (675) and the prevalence of CAD in patients coming to medical attention (676) 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 (677). 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 (678).

Ischemic symptoms are important markers of CAD in the general population. Thus, the prevalence of CAD in middle-aged men with typical angina has been estimated at ≈90%, in those with atypical angina at ≈50%, in those with nonanginal chest pain at ≈16%, and in asymptomatic subjects at ≈4% (676). 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 (376,679), and right ventricular hypertrophy (680). 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, ≈25% in those with atypical chest pain, and ≈20% in those without chest pain (681–688). Even in patients <40 years old with no chest pain and no coronary risk factors, the prevalence of CAD is 3% to 5% (677,688,689). In general, because angina is a poor marker of CAD in patients with AS, coronary arteriography is recommended in symptomatic patients before AVR, especially in men >35 years old, premenopausal women >35 years old with coronary risk factors, and postmenopausal women.

CAD is less prevalent in patients with AR than in those with AS (681–688,690–697), which is related in part to the younger age of patients with AR. The prevalence of CAD in patients with MS (≈20%) is lower than in patients with aortic valve disease (690,692,697–699), 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 as well as those with AS. Thus, in symptomatic patients and/or those with LV dysfunction, preoperative coronary angiography is recommended in men >35, premenopausal women >35 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 III.E.5. of these guidelines. Neither angina nor heart failure symptoms are reliable markers of CAD in these patients. In patients undergoing catheterization to evaluate etiology and severity of MR, CAD is present in ≈33% (700,701). In patients undergoing catheterization for acute ischemic syndromes, ≈20% have associated MR (702). Those with chronic CAD and MR usually have lower LV ejection fractions and more extensive CAD than those without MR (700,703).

B. Diagnosis of Coronary Artery Disease

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 reduce 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 (704–706), as are myocardial perfusion abnormalities induced by exercise or pharmacological stress (707–711). Thus, there are few indications for myocardial perfusion imaging with thallium 201 or technetium 99m perfusion agents in patients with severe valvular disease, and coronary arteriography remains the most appropriate method for the definitive diagnosis of CAD (1). Noninvasive imaging is useful when CAD is suspected in patients with mild valve stenosis or regurgitation and normal LV cavity size and wall thickness.

Recommendations for Coronary Angiography in Patients With Valvular Heart Disease

Indication	*Class*
1. 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** **· Coronary risk factors* (including advanced age)†**	**I**
2. Patients with apparently mild to moderate valvular heart disease but with **· Progressive (Class II or greater) angina** **· Objective evidence of ischemia** **· Decreased LV systolic function** **· Overt congestive heart failure**	**I**
3. Patients undergoing catheterization to confirm the severity of valve lesions before valve surgery without preexisting evidence of CAD, multiple coronary risk factors, or advanced age.†	**IIb**
4. Young patients† undergoing nonemergent valve surgery when no further hemodynamic assessment by catheterization is deemed necessary and no coronary risk factors, no history of CAD, and no evidence of ischemia are present.	**III**
5. Asymptomatic patients with valvular heart disease when valve surgery or balloon commissurotomy is not being considered.	**III**
6. Patients having emergency valve surgery for acute valve regurgitation, aortic root disease, or infective endocarditis when there are no coronary risk factors, angina, objective evidence of ischemia, evidence of coronary embolization, LV systolic dysfunction, or age <35 years.	**III**

***Patients undergoing mitral balloon valvotomy need not undergo coronary angiography based only on coronary risk factors. †The age at which coronary angiography should be performed before valve surgery is difficult to define. The committee recommends coronary angiography in men ≥35 years of age, premenopausal women ≥35 years of age with coronary risk factors, and postmenopausal women.**

C. Treatment of Coronary Artery Disease at the Time of Aortic Valve Replacement

As noted previously, ≥33% of patients with AS undergoing AVR have concomitant CAD. More than 50% of patients >70 years old have CAD. Several studies have reported the outcomes of patients undergoing combined coronary artery bypass surgery and AVR. Although combined myocardial revascularization and AVR increases cross clamp time (712) and has the potential to increase perioperative myocardial infarction and early postoperative mortality in comparison with patients without CAD undergoing isolated AVR (713–716), in several series combined coronary artery bypass surgery has had little or no adverse effect on operative mortality (717–724). Moreover, combined coronary bypass grafting and AVR reduces the rates of perioperative myocardial infarction, operative mortality, and late mortality and morbidity compared with patients with significant CAD who did not undergo revascularization at the time of AVR (723–726). In addition to severity of CAD, the multivariate factors for late postoperative mortality include severity of AS, severity of LV dysfunction, age >70 (especially in women), and presence of NYHA functional Class IV symptoms (724,727,728). Incomplete revascularization is associated with greater postoperative systolic dysfunction (729,730) and reduced survival rates (731) after surgery compared with patients who receive complete revascularization. For over a decade, improved myocardial preservation techniques have been associated with reduced overall operative mortality (732), and it has become standard practice to bypass all significant coronary artery stenoses when possible in patients undergoing AVR. The committee recommends this approach.

D. Aortic Valve Replacement in Patients Undergoing Coronary Artery Bypass Surgery

Patients undergoing coronary artery bypass surgery who have severe AS should undergo AVR at the time of revascularization. Decision making is less clear in patients who have CAD requiring coronary bypass surgery who have mild to moderate AS. Controversy persists regarding the indications for "prophylactic" AVR at the time of coronary bypass surgery in such patients. This decision should be made only after the severity of AS is determined carefully 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, as many such patients may actually have severe AS (as discussed in detail in section III.A. of these guidelines). The more complex and controversial issue is the decision to replace the aortic valve for only mild AS at the time of coronary bypass surgery 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

revascularization surgery. As noted previously (section III.A.3. of these guidelines), 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 (72–84). The average rate of reduction in valve area is ≈0.12 cm^2 per year (84), but the rate of change in an individual patient is difficult to predict.

Retrospective studies of patients who have come to AVR after previous coronary bypass surgery have been reported in whom the mean time to reoperation was 5 to 8 years (733–737). The aortic valve gradient at the primary operation was small, ≤20 mm Hg, but the mean gradient increased significantly to >50 mm Hg at the time of the second operation. It is important to note that these 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 (30 to 50 mm Hg mean gradient at catheterization or 3 to 4 m/s transvalvular velocity by Doppler echocardiography) who are undergoing coronary artery bypass surgery may warrant AVR at the time of revascularization, but this is controversial because there are limited data to indicate the wisdom of this general policy. In most patients with normal stroke volumes and small mean gradients (<30 mm Hg and/or <3 m/s), there is greater controversy regarding AVR at the time of coronary artery bypass surgery, and the strength of this recommendation is reduced.

Recommendations for Aortic Valve Replacement in Patients Undergoing Coronary Artery Bypass Surgery

Indication	*Class*
1. In patients undergoing coronary artery bypass surgergy (CABG) who have severe AS who meet the criteria for valve replacement (section III. of these guidelines).	**I**
2. In patients undergoing CABG who have moderate AS (mean gradient 30 to 50 mm Hg or Doppler velocity 3 to 4 m/s).	**IIa**
3. In patients undergoing CABG who have mild AS (mean gradient <30 mm Hg or Doppler velocity <3 m/s).	**IIb**

E. Management of Concomitant Mitral Valve Disease and Coronary Artery Disease

Most patients with both mitral valvular disease and CAD have ischemic MR, as discussed in section III.E.5. of these guidelines. In patients with 1 to 2+ MR, ischemic symptoms usually dictate the need for revascularization, and the mitral valve is rarely repaired or replaced unless intraoperative echocardiography indicates more severe MR. In patients with more severe MR, the mitral valve is addressed surgically, and all obstructed coronary arteries are revascularized.

In patients with mitral valve disease due to diseases other than ischemia, significantly obstructed coronary arteries identified at preoperative cardiac catheterization are generally revascularized at the time of mitral valve surgery. There are no data to indicate the wisdom of this general policy, but because revascularization usually adds little morbidity or mortality to operation, the additional revascularization surgery is usually recommended.

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