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2014 AHA/ACC Guideline 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

Rick A. Nishimura, Catherine M. Otto, Robert O. Bonow, Blase A. Carabello, John P. Erwin III, Robert A. Guyton, Patrick T. O'Gara, Carlos E. Ruiz, Nikolaos J. Skubas, Paul Sorajja, Thoralf M. Sundt III and James D. Thomas

Circulation. published online March 3, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2014/02/27/CIR.0000000000000031.citation

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2014/03/03/CIR.0000000000000031.DC1.html
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2014 AHA/ACC Guideline 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

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

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This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in January 2014.

The online-only Data Supplement is available with this article at

http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1.

The online-only Comprehensive Relationships With Industry table is available with this article at

http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC2.

The American Heart Association requests that this document be cited as follows:: Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC guideline 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. *Circulation*. 2014; 129:●●●●–●●●●.

This article has been copublished in the *Journal of the American College of Cardiology*.

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(*Circulation*. 2014;129:000–000.)

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Preamble

The medical profession should play a central role in evaluating evidence related to drugs, devices, and procedures for detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist clinicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines (Task Force) directs this effort by developing, updating, and revising practice guidelines for cardiovascular diseases and procedures

Experts in the subject under consideration are selected from both ACC and AHA to examine subject-specific data and write guidelines. Writing committees are specifically charged with performing a literature review, weighing the strength of evidence for or against particular tests, treatments, or procedures, and including estimates of expected health outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered, as well as frequency of follow-up and cost effectiveness. When available, information from studies on cost is considered; however, review of data on efficacy and outcomes constitutes the primary basis for preparing recommendations in this guideline.

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In analyzing the data and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force (1). The Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits, as well as evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as LOE A, B, or C, according to specific definitions. The schema for the COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR. Studies are identified as observational, retrospective, prospective, or randomized, as appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues with sparse available data, a survey of current practice among the clinician members of the writing committee is the basis for LOE C recommendations and no references are cited.

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A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another are included for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term guideline-directed medical therapy (GDMT) to represent optimal medical therapy as defined by ACC/AHA guideline (primarily Class I)-recommended therapies. This new term, GDMT, is used herein and throughout subsequent guidelines.

Because the ACC/AHA practice guidelines address patient populations (and clinicians) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and relevance to the ACC/AHA target population to determine whether the findings should inform a specific recommendation.

The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment about care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas are identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the members of the writing committee. All writing committee members and peer reviewers of the guideline are required to disclose all

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current healthcare-related relationships, including those existing 12 months before initiation of the writing effort.

In December 2009, the ACC and AHA implemented a new RWI policy that requires the writing committee chair plus a minimum of 50% of the writing committee to have no relevant RWI (Appendix 1 includes the ACC/AHA definition of relevance). The Task Force and all writing committee members review their respective RWI disclosures during each conference call and/or meeting of the writing committee, and members provide updates to their RWI as changes occur. All guideline recommendations require a confidential vote by the writing committee and require approval by a consensus of the voting members. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2. Members may not draft or vote on any recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members with specific section recusals noted in Appendix 1. In addition, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC2.

Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The ACC and AHA exclusively sponsor the work of the writing committee without commercial support. Writing committee members volunteered their time for this activity. Guidelines are official policy of both the ACC and AHA.

In an effort to maintain relevance at the point of care for clinicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust* (2, 3). It is noteworthy that the Institute of Medicine cited ACC/AHA practice guidelines as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update, the full-text guideline is revised, or until a published addendum declares it out of date and no longer official ACC/AHA policy.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

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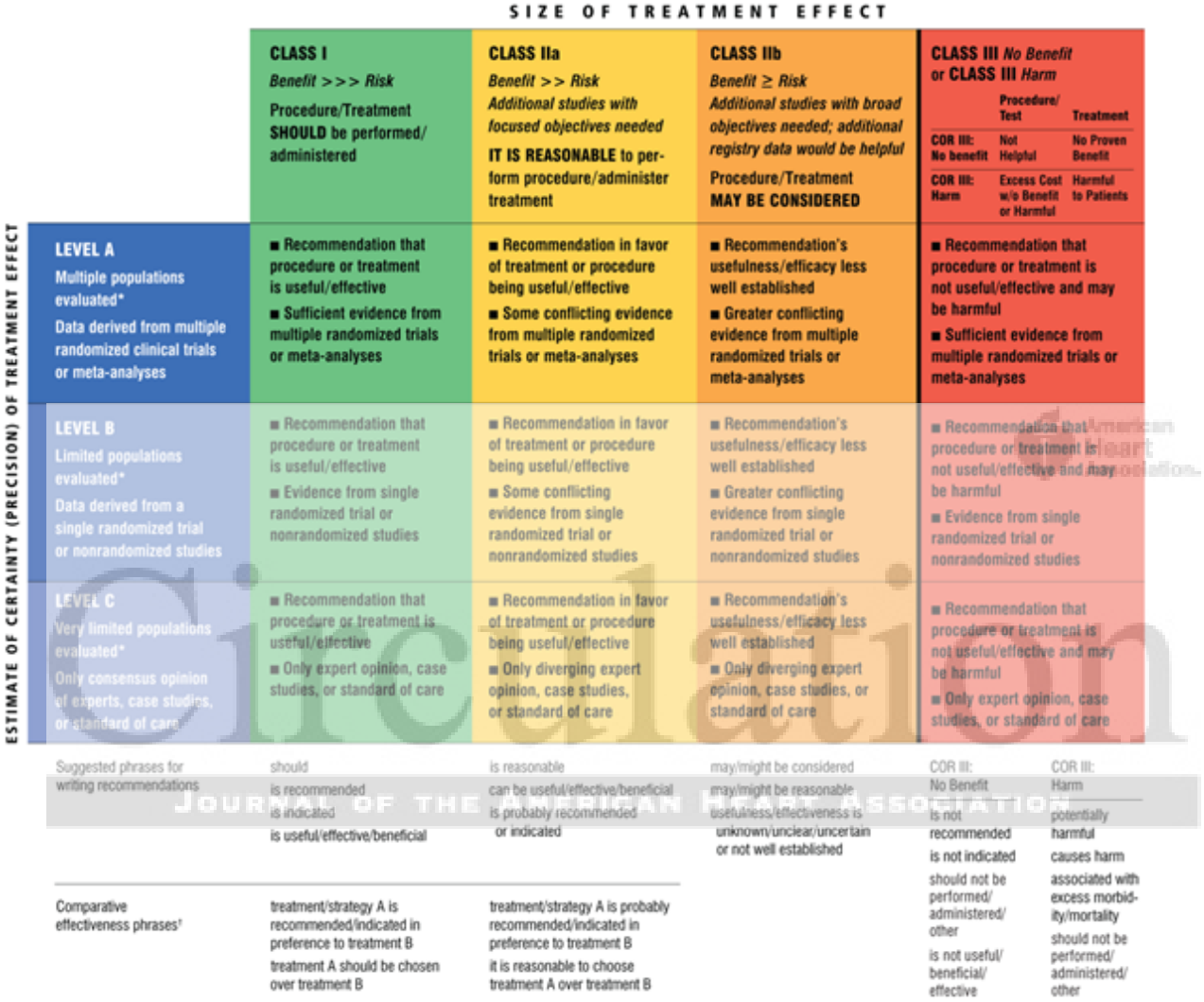
Table 1. Applying Classification of Recommendations and Level of Evidence



A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive review was conducted on literature published through November 2012, and other selected references through October 2013

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were reviewed by the guideline writing committee. Searches were extended to studies, reviews, and other evidence conducted on human subjects and that were published in English from PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *valvular heart disease, aortic stenosis, aortic regurgitation, bicuspid aortic valve, mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation, pulmonic stenosis, pulmonic regurgitation, prosthetic valves, anticoagulation therapy, infective endocarditis, cardiac surgery,* and *transcatheter aortic valve replacement*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACC and AHA. The references selected and published in this document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The committee was composed of clinicians, which included cardiologists, interventionalists, surgeons, and anesthesiologists. The committee also included representatives from the American Association for Thoracic Surgery, American Society of Echocardiography (ASE), Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons (STS).

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by both the ACC and the AHA, as well as 1 reviewer each from the American Association for Thoracic Surgery, ASE, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and STS and 39 individual content reviewers (which included representatives from the following ACC committees and councils: Adult Congenital and Pediatric Cardiology Section, Association of International Governors, Council on Clinical Practice, Cardiovascular Section Leadership Council, Geriatric Cardiology Section Leadership Council, Heart Failure and Transplant Council, Interventional Council, Lifelong Learning Oversight Committee, Prevention of Cardiovascular Disease Committee, and Surgeon Council). Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and AHA and endorsed by the American Association for Thoracic Surgery, ASE, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and STS.

1.4. Scope of the Guideline

The focus of this guideline is the diagnosis and management of adult patients with valvular heart disease (VHD). A full revision of the original 1998 VHD guideline was made in 2006, and an update was made in 2008 (4). Some recommendations from the earlier VHD guidelines have been updated as warranted by new evidence or a better understanding of earlier evidence, whereas others that were inaccurate, irrelevant, or overlapping were deleted or modified. Throughout, our goal was to provide the clinician with concise, evidence-based, contemporary recommendations and the supporting documentation to encourage their use.

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This guideline was created in a different format from prior VHD guidelines to facilitate the access of concise, relevant bytes of information at the point of care when clinical knowledge is needed the most. Thus, each COR is followed by a brief paragraph of supporting text and references. Where applicable, sections were divided into subsections of 1) diagnosis and follow-up, 2) medical therapy, and 3) intervention. The purpose of these subsections was to categorize the COR according to the clinical decision-making pathways that caregivers use in the management of patients with VHD. New recommendations for assessment of the severity of valve lesions have been proposed, based on current natural history studies of patients with VHD.

The present document applies to adult patients with VHD. Management of patients with congenital heart disease and infants and children with valve disease are not addressed here. The document recommends a combination of lifestyle modifications and medications that constitute GDMT. Both for GDMT and other recommended drug treatment regimens, the reader is advised to confirm dosages with product insert material and to carefully evaluate for contraindications and drug–drug interactions. Table 2 is a list of associated guidelines that may be of interest to the reader. The table is intended for use as a resource and obviates the need to repeat already extant guideline recommendations.

Table 2. Associated Guidelines and Statements

Title	Organization	Publication Year/Reference
Recommendations for Evaluation of the Severity of Native Valvular Regurgitation With Two-Dimensional and Doppler Echocardiography	ASE	2003 (5)
Guidelines for the Management of Patients With Atrial Fibrillation	ACC/AHA/ESC	2006 (6)*
Guidelines for the Management of Adults With Congenital Heart Disease	ACC/AHA	2008 (7)
Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice	EAE/ASE	2009 (8)
Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound	ASE	2009 (9)
Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy	ACCF/AHA	2011 (10)
Guidelines on the Management of Cardiovascular Diseases During Pregnancy	ESC	2011 (11)
Antithrombotic and Thrombolytic Therapy for Valvular Disease: Antithrombotic Therapy and Prevention of Thrombosis	ACCP	2012 (12)
Guidelines on the Management of Valvular Heart Disease	ESC/EACTS	2012 (13)
Guideline for the Management of Heart Failure	ACCF/AHA	2013 (14)

*The "ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation" and the 2 subsequent focused updates from 2011 (6, 15, 16) are considered policy at the time of publication of the VHD guideline. However, a fully revised AF guideline is in development and will include updated recommendations on AF; it is expected that the revised AF guideline will be published in 2014.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AHA, American Heart Association; ASE, American Society of Echocardiography; EACTS, European Association of Cardio Thoracic Surgery; EAE, European Association of Echocardiography; ESC, European Society of Cardiology; and VHD, valvular heart disease.

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2. General Principles

2.1. Evaluation of the Patient With Suspected VHD

Patients with VHD may present with a heart murmur, symptoms, or incidental findings of valvular abnormalities on chest imaging or noninvasive testing. Irrespective of the presentation, all patients with known or suspected VHD should undergo an initial meticulous history and physical examination. A careful history is of great importance in the evaluation of patients with VHD, because decisions about treatment are based on the presence or absence of symptoms. Due to the slow, progressive nature of many valve lesions, patients may not recognize symptoms because they may have gradually limited their daily activity levels. A detailed physical examination should be performed to diagnose and assess the severity of valve lesions based on a compilation of all findings made by inspection, palpation, and auscultation. The use of an electrocardiogram (ECG) to confirm heart rhythm and use of a chest x-ray to assess the presence or absence of pulmonary congestion and other lung pathology may be helpful in the initial assessment of patients with known or suspected VHD. A comprehensive transthoracic echocardiogram (TTE) with 2-dimensional (2D) imaging and Doppler interrogation should then be performed to correlate findings with initial impressions based on the initial clinical evaluation. The TTE will also be able to provide additional information, such as the effect of the valve lesion on the cardiac chambers and great vessels, and to assess for other concomitant valve lesions. Other ancillary testing such as transesophageal echocardiography (TEE), computed tomography (CT) or cardiac magnetic resonance (CMR) imaging, stress testing, and diagnostic hemodynamic cardiac catheterization may be required to determine the optimal treatment for a patient with VHD. An evaluation of the possible surgical risk for each individual patient should be performed if intervention is contemplated, as well as other contributing factors such as the presence and extent of comorbidities and frailty. Follow-up of these patients is important and should consist of an annual history and physical examination in most stable patients. An evaluation of the patient may be necessary sooner than annually if there is a change in the patient's symptoms. In some valve lesions, there may be unpredictable adverse consequences on the left ventricle in the absence of symptoms necessitating more frequent follow-up. The frequency of repeat testing, such as echocardiography, will be dependent on the severity of the valve lesion and its effect on the left or right ventricle, coupled with the known natural history of the valve lesion.

2.2. Definitions of Severity of Valve Disease

Classification of the severity of valve lesions should be based on multiple criteria, including the initial findings on the physical examination, which should then be correlated with data from a comprehensive TTE. Intervention should primarily be performed on patients with severe VHD in addition to other criteria outlined in this document.

This document provides a classification of the progression of VHD with 4 stages (A to D) similar to that proposed by the "2013 ACCF/AHA Guideline for the Management of Heart Failure." Indication for intervention in patients with VHD is dependent on 1) the presence or absence of symptoms; 2) the severity of VHD; 3) the response of the left and/or right ventricle to the volume or pressure overload caused by VHD; 4) the effect on

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the pulmonary or systemic circulation; and 5) a change in heart rhythm. The stages take into consideration all of these important factors (Table 3). The criteria for the stages of each individual valve lesion are listed in Section 3 (Table 8), Section 4.2 (Table 11), Section 6.1 (Table 13), Section 7.2 (Tables 15 and 16), and Section 8.1 (Table 19), Section 8.3 (Table 20), Section 9.1 (Table 21), and Section 9.2 (Table 22).

Table 3. Stages of Progression of VHD

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD: C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

VHD indicates valvular heart disease.

The purpose of valvular intervention is to improve symptoms and/or prolong survival, as well as to minimize the risk of VHD-related complications such as asymptomatic irreversible ventricular dysfunction, pulmonary hypertension, stroke, and atrial fibrillation (AF). Thus, the criteria for "severe" VHD are based on studies describing the natural history of patients with unoperated VHD, as well as observational studies relating the onset of symptoms to measurements of severity. In patients with stenotic lesions, there is an additional category of "very severe" stenosis based on studies of the natural history showing that prognosis becomes poorer as the severity of stenosis increases.

Supporting References: (14).

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2.3. Diagnosis and Follow-Up

Diagnostic testing is very important for the diagnosis and treatment of patients with VHD. TTE provides morphological and hemodynamic information for diagnosis and quantitation of VHD, as well as for determining optimal timing for intervention. In selected patients, additional testing such as stress testing, TEE, cardiac catheterization, and CT or CMR imaging might be indicated. However, both the performance and interpretation of these diagnostic tests require meticulous attention to detail as well as expertise in cardiac imaging and evaluation of hemodynamics.

2.3.1. Diagnostic Testing–Initial Diagnosis: Recommendation

Class I

1. **TTE is recommended in the initial evaluation of patients with known or suspected VHD to confirm the diagnosis, establish etiology, determine severity, assess hemodynamic consequences, determine prognosis, and evaluate for timing of intervention (17-32). (*Level of Evidence: B*)**

TTE is now the standard diagnostic test in the initial evaluation of patients with known or suspected VHD. Echocardiographic imaging can accurately assess the morphology and motion of valves and can usually

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determine the etiology of the VHD. TTE can also assess for concomitant disease in other valves and associated abnormalities such as aortic dilation. Left ventricular (LV) chamber size and function can be reliably assessed. It is the LV linear dimensions from echocardiography, either from 2D images or 2D-directed M-mode, that have been used in studies to determine timing of valve operation. Until further studies are available using LV volumes, the recommendations in this guideline will refer to LV dimensions. It is also important to understand the variability in measurements of LV dimensions so that decisions on intervention are based on sequential studies rather than a single study, especially in asymptomatic patients. A semiquantitative assessment of right ventricular (RV) size and function is usually made by a visual subjective analysis. Doppler TTE is used for noninvasive determination of valve hemodynamics. In stenotic lesions, measurements of the peak velocity, as well as calculation of valve gradients and valve area, characterize the severity of the lesion. Hemodynamic measurements can be performed at rest and during provocation. The quantitation of the severity of valve regurgitation is based on multiple hemodynamic parameters using color Doppler imaging of jet geometry, continuous wave Doppler recordings of the regurgitant flow, and pulsed wave Doppler measures of transvalvular volume flow rates and flow reversals in the atria and great vessels. The hemodynamic effect of valve lesions on the pulmonary circulation can be determined using tricuspid regurgitation (TR) velocity to provide a noninvasive measurement of RV systolic pressure. TTE quantitation of valve stenosis and valve regurgitation has been validated against catheterization data, in animal models with direct measures of disease severity, and in prospective clinical studies using valve replacement and mortality as the primary endpoint. On the basis of their value in predicting clinical outcomes, these echocardiographic parameters are now used to determine timing of valve intervention in conjunction with symptom status.

Supporting References: (17-32)

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2.3.2. Diagnostic Testing—Changing Signs or Symptoms: Recommendation

Class I

1. **TTE is recommended in patients with known VHD with any change in symptoms or physical examination findings. (*Level of Evidence: C*)**

Patients with VHD should be instructed to always report any change in symptomatic status. Patients with known VHD who have a change in symptoms should undergo a repeat comprehensive TTE study to determine whether the etiology of the symptoms is due to a progression in the valve lesion, deterioration of the ventricular response to the volume or pressure overload, or another etiology. New signs on physical examination also warrant a repeat TTE. The findings on TTE will be important in determining the timing of intervention.

Supporting References: (33-40)

2.3.3. Diagnostic Testing—Routine Follow-Up: Recommendation

Class I

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1. **Periodic monitoring with TTE is recommended in asymptomatic patients with known VHD at intervals depending on valve lesion, severity, ventricular size, and ventricular function. (*Level of Evidence: C*)**

After initial evaluation of an asymptomatic patient with VHD, the clinician may decide to continue close follow-up. The purpose of close follow-up is to prevent the irreversible consequences of severe VHD that primarily affect the status of the ventricles and pulmonary circulation and may also occur in the absence of symptoms. At a minimum, the follow-up should consist of a yearly history and physical examination. Periodic TTE monitoring also provides important prognostic information. The frequency of a repeat 2D and Doppler echocardiogram is based on the type and severity of the valve lesion, the known rate of progression of the specific valve lesion, and the effect of the valve lesion on the affected ventricle (Table 4). This table does not refer to patients with stage D VHD who will usually undergo intervention, as will other select patient populations with stage C VHD.
Supporting References: (22, 29, 32-35, 37-41)

Table 4. Frequency of Echocardiograms in Asymptomatic Patients With VHD and Normal LV Function

Stage	Valve Lesion			
Stage	Aortic Stenosis*	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Progressive (stage B)	Every 3–5 y (mild severity V_{max} 2.0–2.9 m/s) every 1–2 y (moderate severity V_{max} 3.0–3.9 m/s)	Every 3–5 y (mild severity) Every 1–2 y (moderate severity)	Every 3–5 y (MVA >1.5 cm^2)	Every 3–5 y (mild severity) Every 1–2 y (moderate severity)
Severe (stage C)	Every 6-12 mo (V_{max} ≥4 m/s)	Every 6–12 mo Dilating LV: more frequently	Every 1–2 y (MVA 1.0–1.5 cm^2) Once every year (MVA <1.0 cm^2)	Every 6–12 mo Dilating LV: more frequently

Patients with mixed valve disease may require serial evaluations at intervals earlier than recommended for single valve lesions.
*With normal stroke volume.

LV indicates left ventricle; MVA, mitral valve area; VHD, valvular heart disease; and $V_{max,}$ maximum velocity.

2.3.4. Diagnostic Testing—Cardiac Catheterization: Recommendation

Class I

1. **Cardiac catheterization for hemodynamic assessment is recommended in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between the findings on noninvasive testing and physical examination regarding severity of the valve lesion. (*Level of Evidence: C*)**

Although TTE (and in some instances TEE) is now able to provide the required anatomic and hemodynamic information in most patients with VHD, there is still a subset of patients in whom hemodynamic catheterization is necessary to ensure that the proper decision about treatment is made. TTE may provide erroneous or inadequate information in some patients. Severity of stenosis may be underestimated when imaging is difficult or when the Doppler beam is not directed parallel to the valvular jet velocities. TTE quantitation of valve

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regurgitation shows considerable variability in measurement, and severity of disease may be overestimated or underestimated if image or Doppler data quality is suboptimal. If there are inconclusive, noninvasive data, particularly in the symptomatic patient, or if there is a discrepancy between the noninvasive tests and clinical findings, a hemodynamic cardiac catheterization is indicated. The measurements of valve gradients and cardiac output are important for assessing valve stenosis. Contrast angiography is still useful for a semiquantitative assessment of the severity of regurgitation in those instances in which the noninvasive results are discordant with the physical examination. A major advantage of cardiac catheterization is the measurement of intracardiac pressures and pulmonary vascular resistance, which may further aid in decision making about valve intervention. Diagnostic interventions that can be performed in the catheterization laboratory include the use of dobutamine in low-flow states, pulmonary vasodilators in pulmonary hypertension, and exercise hemodynamics in patients with discrepant symptoms. It must be emphasized that there is no longer a "routine" cardiac catheterization. Patients who come to the catheterization laboratory present complex diagnostic challenges, because the noninvasive testing in these patients has not provided all pertinent information. Thus, hemodynamic catheterization needs to be done with meticulous attention to detail and performed by persons with knowledge and expertise in assessing patients with VHD.

Supporting References: (42, 43)

2.3.5. Diagnostic Testing—Exercise Testing: Recommendation

Class IIa

1. **Exercise testing is reasonable in selected patients with asymptomatic severe VHD to 1) confirm the absence of symptoms, or 2) assess the hemodynamic response to exercise, or 3) determine prognosis (44-48). (*Level of Evidence: B*)**

In a subset of patients, exercise stress testing will be of additional value in determining optimal therapy. Because of the slow, insidious rate of progression of many valve lesions, patients may deny symptoms as they gradually limit their activity level over years to match the gradual limitation imposed by the valve lesion. In patients with an equivocal history of symptoms, exercise testing helps identify those who are truly symptomatic. There may be patients in whom resting hemodynamics do not correlate with symptoms. In these patients, exercise hemodynamics may be helpful in determining the etiology of the symptoms, specifically in patients with mitral VHD. Exercise stress testing is of prognostic value in patients with asymptomatic severe aortic stenosis (AS) and provides further information about timing of intervention. Exercise testing in patients with severe VHD should always be performed by trained operators with continuous monitoring of the ECG and blood pressure (BP).

Supporting References: (44-48)

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2.4. Basic Principles of Medical Therapy

All patients being evaluated for VHD should also undergo GDMT for other risk factors associated with cardiac disease. These include hypertension, diabetes mellitus, and hyperlipidemia. The safety and efficacy of an exercise program for patients with VHD has not been established, but patients will benefit from an exercise prescription in which a regular aerobic exercise program is followed to ensure cardiovascular fitness. Although heavy isometric repetitive training will increase the afterload on the LV, resistive training with small free weights or repetitive isolated muscle training may be used to strengthen individual muscle groups.

Most patients with LV systolic dysfunction and severe VHD should undergo intervention for the valve itself. However, if the decision has been made for medical therapy, these patients should receive the GDMT drug therapy for LV systolic dysfunction, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and beta-adrenergic blockers. Care must be taken to not abruptly lower BP in patients with stenotic lesions.

Rheumatic fever prophylaxis and infective endocarditis (IE) prophylaxis should be given to appropriate groups of patients as outlined in Sections 2.4.1 and 2.4.2. The maintenance of optimal oral health remains the most important component of an overall healthcare program in preventing IE. Influenza and pneumococcal vaccinations should be given to appropriate patient groups with VHD.

Supporting Reference: (49)

2.4.1. Secondary Prevention of Rheumatic Fever: Recommendation

Rheumatic fever is an important cause of VHD. In the United States, acute rheumatic fever has been uncommon since the 1970s. However, there has been an increase in the number of cases of rheumatic fever since 1987. Understanding of the causative organism, group A *Streptococcus*, has been enhanced by the development of kits that allow rapid detection of this organism. Prompt recognition and treatment of streptococcal pharyngitis constitute primary prevention of rheumatic fever. For patients with previous episodes of well-documented rheumatic fever or in those with evidence of rheumatic heart disease, long-term antistreptococcal prophylaxis is indicated for secondary prevention.

Supporting Reference: (50)

Class I

1. **Secondary prevention of rheumatic fever is indicated in patients with rheumatic heart disease, specifically mitral stenosis (MS) (Tables 5 and 6) (50). (*Level of Evidence: C*)**

Recurrent rheumatic fever is associated with a worsening of rheumatic heart disease. However, infection with group A *Streptococcus* does not have to be symptomatic to trigger a recurrence, and rheumatic fever can recur even when the symptomatic infection is treated. Prevention of recurrent rheumatic fever requires long-term antimicrobial prophylaxis rather than recognition and treatment of acute episodes of group A *Streptococcus* pharyngitis. The recommended treatment regimens and duration of secondary prophylaxis are shown in Tables 5

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and 6. In patients with documented VHD, the duration of rheumatic fever prophylaxis should be at least 10 years or until the patient is 40 years of age (whichever is longer).

Table 5. Secondary Prevention of Rheumatic Fever

Agent	Dosage
Penicillin G benzathine	1.2 million units IM every 4 wk*
Penicillin V potassium	200 mg orally BID
Sulfadiazine	1 g orally once daily
Macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine)†	Varies

*Administration every 3 wk is recommended in certain high-risk situations.
†Macrolide antibiotics should not be used in persons taking other medications that inhibit cytochrome *P450 3A*, such as azole antifungal agents, HIV protease inhibitors, and some selective serotonin reuptake inhibitors.
BID indicates twice daily; HIV, human immunodeficiency virus; and IM, intramuscularly.
Adapted from Gerber et al. (50).

Table 6. Duration of Secondary Prophylaxis for Rheumatic Fever

Type	Duration After Last Attack
Rheumatic fever with carditis and residual heart disease (persistent VHD*)	10 y or until patient is 40 y of age (whichever is longer)
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 y or until patient is 21 y of age (whichever is longer)
Rheumatic fever without carditis	5 y or until patient is 21 y of age (whichever is longer)

*Clinical or echocardiographic evidence.
VHD indicates valvular heart diseases.
Adapted from Gerber et al. (50).

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2.4.2. IE Prophylaxis: Recommendations

Because of the lack of published evidence on the use of prophylactic antibiotics to prevent IE, the value of antibiotic prophylaxis has been questioned by several national and international medical societies. Antibiotic prophylaxis is now indicated for only a subset of patients who are at high risk for developing IE and at highest risk for an adverse outcome if IE occurs. The maintenance of optimal oral health care remains the most effective intervention to prevent future valve infection.

Supporting References: (51-53)

Class IIa

1. **Prophylaxis against IE is reasonable for the following patients at highest risk for adverse outcomes from IE before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa (54-56), *(Level of Evidence: B):***
    - **Patients with prosthetic cardiac valves;**
    - **Patients with previous IE;**
    - **Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve; or**
    - **Patients with congenital heart disease with:**
        - **Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits;**

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- **Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure; or**
- **Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.**

The risk of IE is significantly higher in patients with a history of prosthetic valve replacement. Even in those patients at high risk for IE, the evidence for significant reduction in events with prophylaxis is conflicting. This lack of supporting evidence along with the risk of anaphylaxis and increasing bacterial resistance to antimicrobials led to a significant revision in the AHA recommendations for prophylaxis so that only those patients at the highest risk of developing IE (e.g., those with prosthetic valves) should be treated. Furthermore, evidence for prophylaxis has only been found to be reasonable in dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa. In the case of other prosthetic material (excluding surgically created palliative systemic-pulmonary shunts or conduits) such as annuloplasty rings, neochords, Amplatzer devices, and MitraClips, there have been only sporadic case reports of infected devices. Given the low infection rate and scarcity of data, there is no definitive evidence that prophylaxis in these patients is warranted in the absence of the patient having other high risks of intracardiac infection.

There are no randomized controlled trials (RCTs) or large observational cohort studies for prophylaxis in patients with a previous episode of IE, but given the cumulative risks of mortality with repeated infection, the potentially disabling complications from repeated infections, and the relatively low risk of prophylaxis, prophylaxis for IE has been recommended in this high-risk group of patients. IE is substantially more common in heart transplant recipients than in the general population. The risk of IE is highest in the first 6 months after transplantation due to endothelium disruption, high-intensity immunosuppressive therapy, frequent central venous catheter access, and endomyocardial biopsies. If there is a structurally abnormal valve, IE prophylaxis should be continued indefinitely, given the high risk of IE in post-transplant patients.

In patients in whom IE prophylaxis is reasonable, give prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or cause perforation of the oral mucosa. Bacteremia commonly occurs during activities of daily living such as routine brushing of the teeth or chewing. Persons at risk for developing bacterial IE should establish and maintain the best possible oral health to reduce potential sources of bacterial seeding. Optimal oral health is maintained through regular professional dental care and the use of appropriate dental products, such as manual, powered, and ultrasonic toothbrushes; dental floss; and other plaque-removal devices. There is no evidence for IE prophylaxis in gastrointestinal procedures or genitourinary procedures absent known enterococcal infection.

Multiple epidemiological studies show no increase in the rate of IE since adoption of the AHA and European Society of Cardiology guidelines recommending more restrictive use of IE prophylaxis. The NICE (National Institute for Health and Clinical Excellence, United Kingdom) guidelines took an even more radical

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departure from the previous prophylaxis standards in not recommending antibiotic prophylaxis for dental or nondental procedures (e.g., respiratory, gastrointestinal, and genitourinary). Similarly, subsequent epidemiological studies performed in the wake of the NICE guideline revisions have demonstrated no increase in clinical cases or deaths from IE. For the recommended choice of antibiotic regimen when IE prophylaxis is recommended, see http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_307644.pdf.

Supporting References: (50-59)

Class III: No Benefit

1. **Prophylaxis against IE is not recommended in patients with VHD who are at risk of IE for nondental procedures (e.g., TEE, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection (60). (*Level of Evidence: B*)**

The incidence of IE following most procedures in patients with underlying cardiac disease is low, and there is a lack of controlled data supporting the benefit of antibiotic prophylaxis. Furthermore, the indiscriminate use of antibiotics can be associated with the development of resistant organisms, *Clostridium difficile* colitis, unnecessary expense, and drug toxicity. The risk of IE as a direct result of a flexible endoscopic procedure is small. Transient bacteremia may occur during or immediately after endoscopy; however, there are few reports of IE attributable to endoscopy. For most gastrointestinal endoscopic procedures, the rate of bacteremia is 2% to 5%, and organisms typically identified are unlikely to cause IE. The rate of bacteremia does not increase with mucosal biopsy, polypectomy, or sphincterotomy. There are no data to indicate that deep biopsy, such as that performed in the rectum or stomach, leads to a higher rate of bacteremia. The rate of transient bacteremia is more commonly seen in routine activities such as brushing teeth and flossing (20% to 68%), using toothpicks (20% to 40%), and simply chewing food (7% to 51%). Some gastrointestinal procedures, such as esophageal dilation (as high as 45%), sclerotherapy (31%), and endoscopic retrograde cholangiopancreatography (6% to 18%) have higher rates of bacteremia than simple endoscopy. However, no studies indicate reduced rates of IE with antibiotic prophylaxis.

Surgery, instrumentation, or diagnostic procedures that involve the genitourinary tract may cause bacteremia. The rate of bacteremia following urinary tract procedures is high in the presence of urinary tract infection. Sterilization of the urinary tract with antimicrobial therapy in patients with bacteriuria should be attempted before elective procedures, including lithotripsy. Results of a preprocedure urine culture will allow the clinician to choose antibiotics appropriate for the recovered organisms.

Supporting References: (61-73)

2.5. Evaluation of Surgical and Interventional Risk

The decision to intervene, as well as the type of intervention for a patient with severe VHD, should be based on an individual risk–benefit analysis. The risk of the procedure and intermediate-term mortality must be weighed against the benefits of the procedure in altering the natural history of the disease and acknowledging the long-

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term consequences of the intervention. Operative mortality can be estimated from a number of different scoring systems by using a combination of risk factors such as the STS risk estimate or Euroscore (http://www.euroscore.org/). There are limitations to these scores, including that they derive only from surgical patients and that they do not take into consideration procedure-specific impediments, major organ system compromise, comorbidities, or the frailty of the patient. A risk-assessment scheme combining these factors is presented in Table 7. The STS risk estimate is an accepted tool to predict the risk of a surgical operation. In an analysis of aortic valve operations in the STS database from 2002 to 2010, 80% of patients had a predicted risk of mortality (PROM) of <4% and an actual mean mortality rate of 1.4%. Fourteen percent had a PROM of 4% to 8% and an actual mean mortality rate of 5.1%, and 6% of patients had a PROM of >8% and an actual mortality rate of 11.1%. Other factors such as the frailty of the patient, major organ system compromise, and procedure-specific impediments must be taken into consideration. A number of mechanisms to evaluate frailty assess the ability to perform activities of daily living (independence in feeding, bathing, dressing, transferring, toileting, urinary continence, etc.) and measurements of gait speed, grip strength, and muscle mass. Published frailty scores are available, but a limited evaluation may use the following: no frailty (able to perform all activities of daily living and perform a 5-meter walk in <6 seconds), mild degree of frailty (unable to perform 1 activity of daily living or unable to perform a 5-meter walk in <6 seconds), and moderate-to-severe degree of frailty (unable to perform ≥2 activities of daily living). Further research is required to enhance the predictive accuracy of current risk scores, particularly in patients undergoing transcatheter therapy. The overall risks versus benefits should then be discussed with the patient and family using a shared decision-making process.

In addition to the risk classification in Table 7, it is appropriate to defer any type of intervention in patients who will not benefit in terms of symptoms or improved life span from the procedure. This group of patients in whom surgical or transcatheter intervention for severe VHD is futile are those with 1) a life expectancy of <1 year, even with a successful procedure, and 2) those who have a chance of "survival with benefit" of <25% at 2 years. Survival with benefit means survival with improvement by at least 1 New York Heart Association (NYHA) or Canadian Cardiovascular Society class in heart failure (HF) or angina symptoms, improvement in quality of life, or improvement in life expectancy. Those patients with severe frailty may fall into this category.

Supporting References: (41, 74-78)

Table 7. Risk Assessment Combining STS Risk Estimate, Frailty, Major Organ System Dysfunction, and Procedure-Specific Impediments

	Low Risk (Must Meet ALL Criteria in This Column)	**Intermediate Risk (Any 1 Criterion in This Column)**	**High Risk (Any 1 Criterion in This Column)**	**Prohibitive Risk (Any 1 Criterion in This Column)**
STS PROM*	<4% **AND**	4% to 8% **OR**	>8% **OR**	Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 y **OR**
Frailty†	None **AND**	1 Index (mild) **OR**	≥2 Indices (moderate to severe)	

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			OR	
Major organ system compromise not to be improved postoperatively‡	None **AND**	1 Organ system **OR**	No more than 2 organ systems **OR**	≥3 Organ systems **OR**
Procedure-specific impediment§	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

*Use of the STS PROM to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 standard deviation of STS average observed/expected ratio for the procedure in question.
†Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) and independence in ambulation (no walking aid or assist required or 5-meter walk in <6 s). Other scoring systems can be applied to calculate no, mild-, or moderate-to-severe frailty.
‡Examples of major organ system compromise: Cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 <50% or $DLCO_2$ <50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.
§Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage.

CKD indicates chronic kidney disease; CNS, central nervous system; CVA, stroke; $DLCO_2$, diffusion capacity for carbon dioxide; FEV1, forced expiratory volume in 1 s; GI, gastrointestinal; INR, international normalized ratio; LV, left ventricular; PROM, predicted risk of mortality; RV, right ventricular; STS, Society of Thoracic Surgeons; and VKA, vitamin K antagonist.

2.6. The Heart Valve Team and Heart Valve Centers of Excellence: Recommendations

The number of patients presenting with VHD in developed countries is growing, primarily due to the increasing age of the population. In addition, more patients with VHD are referred to cardiovascular specialists due to enhanced awareness of various treatments, as well as improved noninvasive imaging tests. When patients with VHD are referred for intervention in a timely manner, there is an improved outcome in preservation of ventricular function as well as enhanced survival. However, the management of patients with VHD is becoming increasingly complex, due to the use of more sophisticated noninvasive imaging modalities and technological advances in therapies. These advances result in changing thresholds for valve interventions. There remain a number of patients who are referred for intervention too late in the course of their disease or not referred at all, either of which results in poor long-term outcomes. Alternatively, intervention in the asymptomatic patient requires expertise in evaluation and noninvasive imaging assessment. The advent of transcatheter valve therapies has transformed the treatment of elderly high-risk patients with severe VHD but imposes difficult decision making in terms of risk–benefit analysis. Patient care should be customized to the patient's needs, values, and expectations.

A competent practicing cardiologist should have the ability to diagnose and direct the treatment of most patients with VHD. For instance, otherwise healthy patients with severe VHD who become symptomatic should nearly always be considered for intervention. However, more complex decision-making processes may be

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required in select patient populations, such as those who have asymptomatic severe VHD, those who are at high risk for intervention, or those who could benefit from specialized therapies such as valve repair or transcatheter valve intervention.

The management of patients with complex severe VHD is best achieved by a Heart Valve Team composed primarily of a cardiologist and surgeon (including a structural valve interventionist if a catheter-based therapy is being considered). In selected cases, there may be a multidisciplinary, collaborative group of caregivers, including cardiologists, structural valve interventionalists, cardiovascular imaging specialists, cardiovascular surgeons, anesthesiologists, and nurses, all of whom have expertise in the management and outcomes of patients with complex VHD. The Heart Valve Team should optimize patient selection for available procedures through a comprehensive understanding of the risk–benefit ratio of different treatment strategies. This is particularly beneficial in patients in whom there are several options for treatment, such as the elderly high-risk patient with severe symptomatic AS being considered for transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (AVR). The patient and family should be sufficiently educated by the Heart Valve Team about all alternatives for treatment so that their expectations can be met as fully as possible using a shared decision-making approach.

The optimal care of the patient with complex heart disease is best performed in centers that can provide all available options for diagnosis and management, including the expertise for complex aortic or mitral valve repair, aortic surgery, and transcatheter therapies. This has led to the development of Heart Valve Centers of Excellence. Heart Valve Centers of Excellence 1) are composed of experienced healthcare providers with expertise from multiple disciplines; 2) offer all available options for diagnosis and management, including complex valve repair, aortic surgery, and transcatheter therapies; 3) participate in regional or national outcome registries; 4) demonstrate adherence to national guidelines; 5) participate in continued evaluation and quality improvement processes to enhance patient outcomes; and 6) publicly report their available mortality and success rates. Decisions about intervention at the Heart Valve Centers of Excellence should be dependent on the centers' publicly available mortality rates and operative outcomes. It is recognized that some Heart Valve Centers of Excellence may have expertise in select valve problems.

Class I

1. **Patients with severe VHD should be evaluated by a multidisciplinary Heart Valve Team when intervention is considered. (*Level of Evidence: C*)**

Decisions about selection and timing of interventions for patients with severe VHD are best done through the Heart Valve Team. The Heart Valve Team is composed primarily of a cardiologist and surgeon (including a structural valve interventionist if a catheter-based therapy is being considered). In selected cases, there may be a multidisciplinary, collaborative group of caregivers, including cardiologists, structural valve interventionalists, cardiovascular imaging specialists, cardiovascular surgeons, anesthesiologists, and nurses, many of whom have expertise in the management and outcomes of patients with complex VHD. For patients with infections of the

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heart, infectious disease specialists should be involved. For pregnant women, high-risk obstetrics should be involved. The Heart Valve Team 1) reviews the patient's medical condition and valve abnormality, 2) determines the possible interventions that are indicated, technically feasible, and reasonable, and 3) discusses the risks and outcomes of these interventions with the patient and family. This approach has been used for patients with complex coronary artery disease (CAD) and is supported by reports that patients with complex CAD referred specifically for percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in concurrent trial registries using a heart team approach have lower mortality rates than those randomly assigned to PCI or CABG in controlled trials.

Supporting References: (35, 79-84)

Class IIa

1. **Consultation with or referral to a Heart Valve Center of Excellence is reasonable when discussing treatment options for 1) asymptomatic patients with severe VHD, 2) patients who may benefit from valve repair versus valve replacement, or 3) patients with multiple comorbidities for whom valve intervention is considered. (*Level of Evidence: C*)**

With the advent of newer surgical techniques and lower rates of operative mortality, it is reasonable to lower the threshold for valve intervention to prevent the adverse consequences of severe VHD, particularly in the asymptomatic patient with severe VHD. However, the overall benefit of operating on these patients requires that the patient be evaluated by those with expertise in assessment of VHD and that they undergo operation in a center with low operative mortality and excellent patient outcomes. If a "watchful waiting" approach is taken in asymptomatic patients with severe VHD, a Heart Valve Center of Excellence may be beneficial in ensuring proper follow-up.

Surgical outcomes depend on the expertise and experience of the surgeons, especially with highly specialized operations such as complex mitral valve repair and surgical treatment of aortic disease. It is well documented that operative risks and outcomes are better for patients undergoing mitral valve repair versus mitral valve replacement (MVR) in patients with primary mitral regurgitation (MR) and morphology suitable for repair. Although the rate of mitral valve repair has increased, a number of patients with primary MR will still undergo MVR. The rate of successful mitral valve repair in patients with primary MR is dependent on the experience of the surgeon as well as the surgical volume. Optimal outcomes are best achieved in Heart Valve Centers of Excellence dedicated to the management and treatment of patients with VHD and that offer all available treatment options, including complex valve repair, aortic surgery, and transcatheter therapies. At Heart Valve Centers of Excellence, healthcare providers have experience and expertise from multiple disciplines, demonstrate adherence to national guidelines, participate in regional or national outcome registries, and publicly report their available mortality and success rates with a continued quality improvement program in place. Decisions on early operation in the asymptomatic patient can then be made based on the reported data from the specific Heart Valve Center of Excellence, including mortality and morbidity statistics as well as durable repair rates for patients with primary MR. Heart Valve Centers of Excellence have also been shown to increase the

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proportion of patients managed according to GDMT, decrease unnecessary testing, optimize timing of intervention, and best handle other problems such as operations for complex multivalve disease, multiple reoperations, and complex IE. Heart Valve Centers of Excellence can play an important role in patient and clinician education to help ensure timely referral for evaluation and proper protocol for follow-up.

Supporting References: (35, 85-88)

3. Aortic Stenosis

See Table 8 for the stages of valvular AS and Tables 9 and 10 for a summary of recommendations for choice and timing of intervention.

3.1. Stages of Valvular AS

Medical and interventional approaches to the management of patients with valvular AS depend on accurate diagnosis of the cause and stage of the disease process. Table 8 shows the stages of AS ranging from patients at risk of AS (stage A) or with progressive hemodynamic obstruction (stage B) to severe asymptomatic (stage C) and symptomatic AS (stage D). Each of these stages is defined by valve anatomy, valve hemodynamics, the consequences of valve obstruction on the left ventricle and vasculature, as well as by patient symptoms. Hemodynamic severity is best characterized by the transaortic maximum velocity (or mean pressure gradient) when the transaortic volume flow rate is normal. However, some patients with AS have a low transaortic volume flow rate due to either LV systolic dysfunction with a low LV ejection fraction (LVEF) or due to a small hypertrophied left ventricle with a low stroke volume. These categories of severe AS pose a diagnostic and management challenge distinctly different from the majority of patients with AS who have a high gradient and velocity when AS is severe. These special subgroups with low-flow AS are designated D2 (with a low LVEF) and D3 (with a normal LVEF).

The definition of severe AS is based on natural history studies of patients with unoperated AS, which show that the prognosis is poor once there is a peak aortic valve velocity of >4 m per second, corresponding to a mean aortic valve gradient >40 mm Hg. In patients with low forward flow, severe AS can be present with lower aortic valve velocities and lower aortic valve gradients. Thus, an aortic valve area should be calculated in these patients. The prognosis of patients with AS is poorer when the aortic valve area is <1.0 cm^2. At normal flow rates, an aortic valve area of <0.8 cm^2 correlates with a mean aortic valve gradient >40 mm Hg. However, symptomatic patients who have a calcified aortic valve with reduced opening and an aortic valve area between 0.8 cm^2 and 1.0 cm^2 should be closely evaluated to determine whether they would benefit from valve intervention. Meticulous attention to detail is required when assessing aortic valve hemodynamics, either with Doppler echocardiography or cardiac catheterization, and the inherent variability of the measurements and calculations should always be considered in clinical-decision making.

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Table 8. Stages of Valvular AS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk of AS**	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis	• Aortic V_{max} <2 m/s	• None	• None
B	**Progressive AS**	• Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or • Rheumatic valve changes with commissural fusion	• Mild AS: Aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mm Hg • Moderate AS: Aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	• Early LV diastolic dysfunction may be present • Normal LVEF	• None
C: Asymptomatic severe AS					
C1	**Asymptomatic severe AS**	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) • Very severe AS is an aortic V_{max} ≥5 m/s or mean ΔP ≥60 mm Hg	• LV diastolic dysfunction • Mild LV hypertrophy • Normal LVEF	• None: Exercise testing is reasonable to confirm symptom status
C2	**Asymptomatic severe AS with LV dysfunction**	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2)	• LVEF <50%	• None
D: Symptomatic severe AS					
D1	**Symptomatic severe high-gradient AS**	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) but may be larger with mixed AS/AR	• LV diastolic dysfunction • LV hypertrophy • Pulmonary hypertension may be present	• Exertional dyspnea or decreased exercise tolerance • Exertional angina • Exertional syncope or presyncope
D2	**Symptomatic severe low-flow/low-gradient AS with reduced LVEF**	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1.0 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg • Dobutamine stress echocardiography shows AVA ≤1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	• LV diastolic dysfunction • LV hypertrophy • LVEF <50%	• HF • Angina • Syncope or presyncope
D3	**Symptomatic severe low-gradient**	• Severe leaflet calcification	• AVA ≤1.0 cm^2 with aortic V_{max} <4 m/s or	• Increased LV	• HF

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	AS with normal LVEF or paradoxical low-flow severe AS	with severely reduced leaflet motion	mean ΔP <40 mm Hg • Indexed AVA ≤0.6 cm^2/m^2 and • Stroke volume index <35 mL/m^2 • Measured when patient is normotensive (systolic BP <140 mm Hg)	relative wall thickness • Small LV chamber with low stroke volume • Restrictive diastolic filling • LVEF ≥50%	• Angina • Syncope or presyncope

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; BP, blood pressure; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; ΔP, pressure gradient; and V_{max}, maximum aortic velocity.

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3.2. Aortic Stenosis

3.2.1. Diagnosis and Follow-Up

The overall approach to the initial diagnosis of VHD is discussed in Section 2.3, and additional considerations specific to patients with AS are addressed here.

3.2.1.1. Diagnostic Testing—Initial Diagnosis: Recommendations

Class I

1. **TTE is indicated in patients with signs or symptoms of AS or a bicuspid aortic valve for accurate diagnosis of the cause of AS, hemodynamic severity, LV size and systolic function, and for determining prognosis and timing of valve intervention (24, 25, 89).** ***(Level of Evidence: B)***

Most patients with AS are typically first diagnosed when cardiac auscultation reveals a systolic murmur or after a review of TTE requested for other indications. Physical examination findings are specific but not sensitive for evaluation of stenosis severity. The classic findings of a loud (grade 3/6 or greater), late-peaking systolic murmur that radiates to the carotid arteries, a single or paradoxically split second heart sound, and a delayed and diminished carotid upstroke confirm the presence of severe AS. However, carotid upstroke may be normal in elderly patients because of the effects of aging on the vasculature, and the murmur may be soft or may radiate to the apex. The only physical examination finding that is reliable in excluding the possibility of severe AS is a normally split second heart sound.

TTE is indicated when there is an unexplained systolic murmur, a single second heart sound, a history of a bicuspid aortic valve, or symptoms that might be due to AS. Echocardiographic imaging allows reliable identification of the number of valve leaflets along with qualitative assessment of valve motion and leaflet calcification. In nearly all patients, the hemodynamic severity of the stenotic lesion can be defined with Doppler echocardiographic measurements of maximum transvalvular velocity, mean pressure gradient, and continuity equation valve area, as discussed in the European Association of Echocardiography (EAE)/ASE guidelines for evaluation of valve stenosis. Doppler evaluation of severity of AS has been well validated in experimental and human studies compared with direct measurements of intracardiac pressure and cardiac output. In addition, Doppler measures of severity of AS are potent predictors of clinical outcome. However, Doppler may underestimate or overestimate aortic velocity and disease severity in some patients, so clinical evaluation should include symptoms, physical examination findings, and results of other diagnostic testing as well.

TTE is also useful for determining the LV response to pressure overload. Systolic function is evaluated using 2D or 3-dimensional (3D) measurement of LVEF. LV diastolic function can be evaluated using standard Doppler approaches and an estimate of pulmonary systolic pressure derived from the TR jet. In addition, TTE allows diagnosis and evaluation of concurrent valve lesions, with MR being common in patients with AS.
Supporting References: (8, 19, 24, 25, 27, 89-94)

Class IIa

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1. **Low-dose dobutamine stress testing using echocardiographic or invasive hemodynamic measurements is reasonable in patients with stage D2 AS with all of the following (95-97), *(Level of Evidence: B):***
    a. **Calcified aortic valve with reduced systolic opening;**
    b. **LVEF less than 50%;**
    c. **Calculated valve area 1.0 cm^2 or less; and**
    d. **Aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg.**

Patients with severe AS and concurrent LV systolic dysfunction often present with a relatively low transvalvular velocity and pressure gradient (i.e., mean pressure gradient <40 mm Hg) but with a small calculated valve area. In some of these patients, severe AS is present with LV systolic dysfunction due to afterload mismatch. In others, primary myocardial dysfunction is present with only moderate AS and reduced aortic leaflet opening due to a low transaortic volume flow rate. In these patients with low-flow/low-gradient AS and LV systolic dysfunction (LVEF <50%), it may be useful to measure aortic velocity (or mean pressure gradient) and valve area during a baseline state and again during low-dose pharmacological (i.e., dobutamine infusion) stress testing to determine whether AS is severe or only moderate and to evaluate for contractile or flow reserve.

Dobutamine is infused in progressive stages, beginning at 5 mcg/kg per minute and increasing in increments of 5 mcg/kg per minute to a maximum dose of 20 mcg/kg per minute with appropriate clinical and hemodynamic monitoring. Echocardiographic and Doppler data (or hemodynamic data) are recorded at each dose of dobutamine for measurement of aortic velocity, mean pressure gradient, valve area, and LVEF. Patients who do not have true anatomically severe AS will exhibit an increase in valve area with only a modest increase in transaortic velocity or gradient as transaortic stroke volume increases. In contrast, patients with severe AS have a relatively fixed valve area even with an increase in LV contractility and transaortic volume flow rate. The document "Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice" defines severe AS on low-dose dobutamine stress testing as a maximum velocity ≥4.0 m per second with a valve area ≤1.0 cm^2 at any point during the test protocol. In addition to moderate AS and true severe AS, low-dose dobutamine stress testing helps identify a third group of patients who fail to show an increase in stroke volume ≥20% with dobutamine, referred to as "lack of contractile reserve" or "lack of flow reserve." This subgroup of patients appears to have a very poor prognosis with either medical or surgical therapy. Low-dose dobutamine stress testing in patients with AS requires center experience in pharmacological stress testing as well as continuous hemodynamic and electrocardiographic monitoring with a cardiologist in attendance.
Supporting References: (8, 43, 95, 96, 98-101)

See Online Data Supplement 1 for more information on outcomes in patients with low-flow/low-gradient AS with reduced LVEF (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

3.2.1.2. Diagnostic Testing—Changing Signs or Symptoms

In patients with known valvular AS, repeat TTE is appropriate when physical examination reveals a louder systolic murmur or a change in the second heart sound or when symptoms occur that might be due to AS because valve obstruction may have progressed since the last evaluation. Repeat TTE is also appropriate in

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patients with AS who are exposed to increased hemodynamic demands either electively, such as noncardiac surgery or pregnancy, or acutely, such as with a systemic infection, anemia, or gastrointestinal bleeding. In these clinical settings, knowledge of the severity of valve obstruction and LV function is critical for optimizing loading conditions and maintaining a normal cardiac output.

Supporting References: (24, 25, 89, 102, 103)

3.2.1.3. Diagnostic Testing—Routine Follow-Up

Timing of periodic clinical evaluation of patients with severe asymptomatic AS depends on comorbidities and patient-specific factors. TTE for reevaluation of asymptomatic patients with AS with normal LV systolic function who have no change in signs or symptoms is performed at intervals of 6 months to 1 year when aortic velocity is ≥4.0 m per second (stage C), 1 to 2 years when aortic velocity is between 3.0 m per second and 3.9 m per second (stage B), and 3 to 5 years when aortic velocity is 2.0 m per second to 2.9 m/s (stage B) (Table 4).

Valvular AS is a progressive disease, and an increase in hemodynamic severity is inevitable once even mild AS is present. The rate of progression of the stenotic lesion has been estimated in a variety of invasive and noninvasive studies. When severe AS is present (aortic velocity ≥4.0 m per second), the rate of progression to symptoms is high, with an event-free survival of only 30% to 50% at 2 years. Therefore, patients with asymptomatic severe AS require frequent monitoring for progressive disease because symptom onset may be insidious and not recognized by the patient.

Once even moderate AS is present (aortic velocity between 3.0 m per second and 3.9 m per second), the average rate of progression is an increase in velocity of 0.3 m per second per year, an increase in mean pressure gradient of 7 mm Hg per year, and a decrease in valve area of 0.1 cm^2 per year. There is marked individual variability in the rate of hemodynamic change. Progression of AS can be more rapid in older patients and in those with more severe leaflet calcification. Because it is not possible to predict the exact rate of progression in an individual patient, regular clinical and echocardiographic follow-up is mandatory in all patients with asymptomatic mild-to-moderate AS.

In patients with aortic sclerosis, defined as focal areas of valve calcification and leaflet thickening with an aortic velocity <2.5 m per second, progression to severe AS occurs in about 10% of patients within 5 years. Patients with bicuspid aortic valve disease are also at risk for progressive valve stenosis, with AS being the most common reason for intervention in patients with a bicuspid aortic valve (Section 5.1.1).

Supporting References: (28, 104-115)

See Online Data Supplement 2 for more information on hemodynamic progression of AS (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

3.2.1.4. Diagnostic Testing—Cardiac Catheterization

Diagnostic TTE and Doppler data can be obtained in nearly all patients, but severity of AS may be underestimated if image quality is poor or if a parallel intercept angle is not obtained between the ultrasound

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beam and aortic jet. CMR imaging shows promise for evaluation of severity of AS but is not widely available. Cardiac CT imaging is useful for quantitation of valve calcification (severe calcification is considered to be present with an aortic valve calcification score >1,000 Agatston units) and in patients undergoing TAVR for measurement of annulus area, leaflet length, and the annular to coronary ostial distance. However, CT imaging is less useful for evaluation of severity of AS. When noninvasive data are nondiagnostic or if there is a discrepancy between clinical and echocardiographic evaluation, cardiac catheterization for determination of severity of AS, is recommended. Transaortic pressure gradients should be recorded for measurement of mean transaortic gradient, based on simultaneous LV and aortic pressure measurements. Aortic valve area should be calculated with the Gorlin formula, using a Fick or thermodilution cardiac output measurement. See Section 14.1 for recommendations on coronary angiography in patients with AS.

Supporting References: (42, 116)

3.2.1.5. Diagnostic Testing—Exercise Testing: Recommendations

Class IIa

1. **Exercise testing is reasonable to assess physiological changes with exercise and to confirm the absence of symptoms in asymptomatic patients with a calcified aortic valve and an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher (stage C) (25, 46, 47, 117). *(Level of Evidence: B)***

When performed under the direct supervision of an experienced clinician, with close monitoring of BP and ECG, exercise testing in asymptomatic patients is relatively safe and may provide information that is not evident during the initial clinical evaluation, particularly when the patient's functional capacity is unclear. Patients with symptoms provoked by exercise testing should be considered symptomatic, even if the clinical history is equivocal. Although it can be challenging to separate normal exercise limitations from abnormal symptoms due to AS, particularly in elderly sedentary patients, exercise-induced angina, excessive dyspnea early in exercise, dizziness, or syncope are consistent with symptoms of AS. In 1 series, exercise testing brought out symptoms in 29% of patients who were considered asymptomatic before testing; in these patients, spontaneous symptoms developed over the next year in 51% of patients, compared with only 11% of patients who had no symptoms on exercise testing.

Exercise testing can also identify a limited exercise capacity, abnormal BP response, or arrhythmia. An abnormal hemodynamic response (e.g., hypotension or failure to increase BP with exercise) in patients with severe AS is considered a poor prognostic finding. In another series, patients with AS who manifested symptoms, an abnormal BP response (<20 mm Hg increase), or ST-segment abnormalities with exercise had a significantly reduced symptom-free survival at 2 years (19% compared with 85%). However, electrocardiographic ST-segment depression is seen in >80% of patients with AS with exercise and is nonspecific for diagnosis of CAD. Ventricular tachycardia was reported in early exercise studies but has not been reported in contemporary series.

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Some studies suggest additional value for measuring changes in valve hemodynamics with exercise. In a series of 186 patients with moderate-to-severe AS, stress testing was normal in 73% of patients; however, adverse cardiac events occurred in 67 of these patients at a mean follow-up interval of 20±14 months. Predictors of cardiac events, primarily symptom onset requiring AVR, were age >65 years, diabetes mellitus, LV hypertrophy, a resting mean pressure gradient >35 mm Hg, and an increase of >20 mm Hg in mean pressure gradient with exercise. However, a prospective study of 123 patients with asymptomatic AS did not show additive value for exercise hemodynamics for predicting clinical outcome when baseline measures of hemodynamic severity and functional status were considered. Recording hemodynamics with exercise is challenging, and simpler parameters are adequate in most patients.

Supporting References: (25, 28, 46, 47, 117-121)

See Online Data Supplement 3 for more information on exercise testing in patients with AS (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class III: Harm

1. **Exercise testing should not be performed in symptomatic patients with AS when the aortic velocity is 4.0 m per second or greater or mean pressure gradient is 40 mm Hg or higher (stage D) (122). *(Level of Evidence: B)***

As reported in several prospective and retrospective studies, the risk of exercise testing is low in asymptomatic patients with AS. However, even in asymptomatic patients, complications include exertional hypotension in up to 10% of patients, exercise-induced symptoms, and ventricular premature beats. A retrospective study of 347 patients with AS who underwent cardiopulmonary exercise testing showed no deaths or major complications. Most of these patients had no (78%) or equivocal (16%) symptoms at baseline, with only 20 symptomatic patients (6%) with AS in this series (123).

Exercise testing should not be performed in symptomatic patients with AS owing to a high risk of complications, including syncope, ventricular tachycardia, and death. In a prospective survey of 20 medical centers in Sweden that included 50,000 exercise tests done over an 18-month period, the complication rate was 18.4; morbidity rate, 5.2; and mortality rate, 0.4 per 10,000 tests. Although the number of patients with AS was not reported, 12 of the 92 complications occurred in patients with AS: 8 had an exercise decline in BP, 1 had asystole, and 3 had ventricular tachycardia.

Supporting References: (46, 47, 117-120, 122, 123)

3.2.2. Medical Therapy: Recommendations

Class I

1. **Hypertension in patients at risk for developing AS (stage A) and in patients with asymptomatic AS (stages B and C) should be treated according to standard GDMT, started at a low dose, and gradually titrated upward as needed with frequent clinical monitoring (124-126). *(Level of Evidence: B)***

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Hypertension is common in patients with AS, may be a risk factor for AS, and adds to the total pressure overload on the left ventricle in combination with valve obstruction. Concern that antihypertensive medications might result in a fall in cardiac output has not been corroborated in studies of medical therapy, including 2 small RCTs, likely because AS does not result in "fixed" valve obstruction until late in the disease process. In 1,616 patients with asymptomatic AS in the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study, hypertension (n=1,340) was associated with a 56% higher rate of ischemic cardiovascular events and a 2-fold increased mortality rate (both $p<0.01$) compared with normotensive patients with AS, although no impact on AVR was seen. Medical therapy for hypertension should follow standard guidelines, starting at a low dose and gradually titrating upward as needed to achieve BP control. There are no studies addressing specific antihypertensive medications in patients with AS, but diuretics should be avoided if the LV chamber is small, because even smaller LV volumes may result in a fall in cardiac output. In theory, ACE inhibitors may be advantageous due to the potential beneficial effects on LV fibrosis in addition to control of hypertension. Beta blockers are an appropriate choice in patients with concurrent CAD.

Supporting References: (124-128)

Class IIb

1. **Vasodilator therapy may be reasonable if used with invasive hemodynamic monitoring in the acute management of patients with severe decompensated AS (stage D) with NYHA class IV HF symptoms.** ***(Level of Evidence: C)***

In patients who present with severe AS and NYHA class IV HF, afterload reduction may be used in an effort to stabilize the patient before urgent AVR. Invasive monitoring of LV filling pressures, cardiac output, and systemic vascular resistance is essential because of the tenuous hemodynamic status of these patients, in whom a sudden decline in systemic vascular resistance might result in an acute decline in cardiac output across the obstructed aortic valve. However, some patients do benefit with an increase in cardiac output as systemic vascular resistance is slowly adjusted downward due to the reduction in total LV afterload. AVR should be performed as soon as feasible in these patients.

Supporting Reference: (129)

Class III: No Benefit

1. **Statin therapy is not indicated for prevention of hemodynamic progression of AS in patients with mild-to-moderate calcific valve disease (stages B to D) (109, 130, 131).** ***(Level of Evidence: A)***

Despite experimental models and retrospective clinical studies that suggest that lipid-lowering therapy with a statin might prevent disease progression of calcific AS, 3 large well-designed RCTs failed to show a benefit either in terms of changes in hemodynamic severity or in clinical outcomes in patients with mild-to-moderate valve obstruction. Thus, at the time of publication, there are no data to support the use of statins for prevention

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of progression of AS. However, concurrent CAD is common in patients with AS, and all patients should be screened and treated for hypercholesterolemia using GDMT for primary and secondary prevention of CAD.

Supporting References: (109, 130-133)

See Online Data Supplement 4 for more information on clinical trials of lipid-lowering therapy to slow progression of AS (stage B) and prevent cardiovascular outcomes (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

3.2.3. Timing of Intervention: Recommendations

See Table 9 for a summary of recommendations from this section and Figure 1 for indications for AVR in patients with AS. These recommendations for timing of intervention for AS apply to both surgical and transcatheter AVR. The integrative approach to assessing risk of surgical or transcatheter AVR is discussed in Section 2.5. The specific type of intervention for AS is discussed in Section 3.2.4.

Table 9. Summary of Recommendations for AS: Timing of Intervention

Recommendations	COR	LOE	References
AVR is recommended with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1)	I	B	(9, 91, 134, 135)
AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF <50%	I	B	(136, 137)
AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery	I	B	(108, 138)
AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥5.0 m/s) and low surgical risk	IIa	B	(139, 140)
AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP	IIa	B	(25, 47)
AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/s (or mean pressure gradient ≥40 mm Hg) with a valve area ≤1.0 cm^2 at any dobutamine dose	IIa	B	(43, 141, 142)
AVR is reasonable in symptomatic patients who have low-flow/low-gradient severe AS (stage D3) who are normotensive and have an LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa	C	N/A
AVR is reasonable for patients with moderate AS (stage B) (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery	IIa	C	N/A
AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk	IIb	C	N/A

AS indicates aortic stenosis; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; COR, Class of Recommendation; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; and N/A, not applicable.

Class I

1. **AVR is recommended in symptomatic patients with severe AS (stage D1) with (91, 134, 135, 143), *(Level of Evidence: B)*:**
    a. **Decreased systolic opening of a calcified or congenitally stenotic aortic valve; and**
    b. **An aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher; and**
    c. **Symptoms of HF, syncope, exertional dyspnea, angina, or presyncope by history or on exercise testing.**

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Hemodynamic progression eventually leading to symptom onset occurs in nearly all asymptomatic patients with AS. However, survival during the asymptomatic phase is similar to age-matched controls with a low risk of sudden death (<1% per year) when patients are followed prospectively and promptly report symptom onset. The rate of symptom onset is strongly dependent on severity of AS, with an event-free survival rate of about 75% to 80% at 2 years in those with a jet velocity <3.0 m per second compared with only 30% to 50% in those with a jet velocity ≥4.0 m per second. Patients with asymptomatic AS require periodic monitoring for development of symptoms and progressive disease, but routine AVR is not recommended (Section 3.1).

However, once even mild symptoms caused by severe AS are present, outcomes are extremely poor unless outflow obstruction is relieved. Typical initial symptoms are dyspnea on exertion or decreased exercise tolerance. The classical symptoms of syncope, angina, and HF are late manifestations of disease, most often seen in patients in whom early symptom onset was not recognized and intervention was inappropriately delayed. In patients with severe, symptomatic, and calcific AS, the only effective treatment is surgical or transcatheter AVR, resulting in improved survival rates, reduced symptoms, and improved exercise capacity. In the absence of serious comorbid conditions that limit life expectancy or quality of life, AVR is indicated in virtually all symptomatic patients with severe AS and should be performed promptly after onset of symptoms. Age alone is not a contraindication to surgery, with several series showing outcomes similar to age-matched normal subjects in the very elderly.

Severe AS is defined as an aortic velocity ≥4.0 m per second or mean pressure gradient ≥40 mm Hg based on outcomes in a series of patients with AS of known hemodynamic severity. Although transaortic velocity and mean pressure gradient are redundant measures of AS severity—with native valve AS there is a close linear correlation between velocity and mean pressure gradient whether measured by catheterization or Doppler methods—both are included in this guideline so that either Doppler or invasive measurements can be used in decision making. There is substantial overlap in hemodynamic severity between asymptomatic and symptomatic patients, and there is no single parameter that indicates the need for AVR. Instead, it is the combination of symptoms, valve anatomy, and hemodynamics (Table 8) that provides convincing evidence that AVR will be beneficial in an individual patient. Many patients with a high transaortic velocity/pressure gradient will remain asymptomatic for several years and do not require AVR until symptom onset. However, if symptoms are present, a high velocity/gradient confirms valve obstruction as the cause of symptoms. With mixed stenosis and regurgitation, a high velocity/gradient indicates severe mixed aortic valve disease. Calculation of valve area is not necessary when a high velocity/gradient is present and the valve is calcified and immobile; most patients will have a valve area ≤1.0 cm^2 or an indexed valve area ≤0.6 cm^2/m^2, but some will have a larger valve area due to a large body size or coexisting aortic regurgitation (AR). Thus, the primary criterion for the definition of severity of AS is based on aortic velocity or mean pressure gradient. Calculations of valve area may be supportive but are not necessary when a high velocity or gradient is present. In contrast,

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valve area calculations are essential for patients with AS and a low ejection fraction or stroke volume as defined for stages D2 and D3.

Supporting References: (24, 25, 29, 89, 92, 94, 108, 109, 134, 135, 139, 140, 144-149)

See Online Data Supplements 5, 6, and 7 for more information on clinical outcomes with asymptomatic AS (stages B and C) of known hemodynamic severity, incidence of sudden death in asymptomatic patients with AS (stages B and C), and clinical outcomes with symptomatic AS of known hemodynamic severity, respectively (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

2. **AVR is recommended for asymptomatic patients with severe AS (stage C2) and an LVEF less than 50% with decreased systolic opening of a calcified aortic valve with an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher (136, 137). *(Level of Evidence: B)***

In patients with a low LVEF and severe AS, survival is better in those who undergo AVR than in those treated medically. The depressed LVEF in many patients is caused by excessive afterload (afterload mismatch), and LV function improves after AVR in such patients. If LV dysfunction is not caused by afterload mismatch, survival is still improved, likely because of the reduced afterload with AVR, but improvement in LV function and resolution of symptoms might not be complete after AVR.

Supporting References: (98, 136, 141, 142, 150-154)

See Online Data Supplement 1 for more information on outcomes in patients with low-flow/low-gradient AS with reduced LVEF (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

3. **AVR is indicated for patients with severe AS (stage C or D) when undergoing cardiac surgery for other indications when there is decreased systolic opening of a calcified aortic valve and an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher (108, 138). *(Level of Evidence: B)***

Prospective clinical studies demonstrate that disease progression occurs in nearly all patients with severe asymptomatic AS. Symptom onset within 2 to 5 years is likely when aortic velocity is ≥4.0 m per second or mean pressure gradient is ≥40 mm Hg. The additive risk of AVR at the time of other cardiac surgery is less than the risk of reoperation within 5 years.

Supporting References: (108, 138, 155, 156)

Class IIa

1. **AVR is reasonable for asymptomatic patients with very severe AS (stage C1) with (139, 140), *(Level of Evidence: B)*:**
    a. **Decreased systolic opening of a calcified valve;**
    b. **An aortic velocity 5.0 m per second or greater or mean pressure gradient 60 mm Hg or higher; and**
    c. **A low surgical risk.**

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In patients with very severe AS and an aortic velocity ≥5.0 m per second or mean pressure gradient ≥60 mm Hg, the rate of symptom onset is approximately 50% at 2 years. Several observational studies have shown higher rates of symptom onset and major adverse cardiac events in patients with very severe, compared with severe, AS. In addition, a study comparing early surgery with surgery at symptom onset in 57 propensity score–matched pairs showed a lower all-cause mortality risk with early surgery (hazard ratio [HR]: 0.135; 95% confidence interval [CI]: 0.030 to 0.597; p=0.008). Thus, it is reasonable to consider elective AVR in patients with very severe asymptomatic AS if surgical risk is low rather than waiting for symptom onset. A low surgical risk is defined as an STS PROM score of <4.0 in the absence of other comorbidities or advanced frailty. At Heart Valve Centers of Excellence, this corresponds to an operative mortality of <1.5% (Section 2.5). Patient age, avoidance of patient-prosthesis mismatch, anticoagulation issues, and patient preferences should be taken into account in a decision to proceed with AVR or continue watchful waiting.

Supporting References (115, 139, 140, 146, 157-159)*:*

Class IIa

2. **AVR is reasonable in apparently asymptomatic patients with severe AS (stage C1) with (25, 47), *(Level of Evidence: B)*:**
    a. **A calcified aortic valve;**
    b. **An aortic velocity of 4.0 m per second to 4.9 m per second or mean pressure gradient of 40 mm Hg to 59 mm Hg; and**
    c. **An exercise test demonstrating decreased exercise tolerance or a fall in systolic BP.**

Exercise testing may be helpful in clarifying symptom status in patients with severe AS. When symptoms are provoked by exercise testing, the patient is considered symptomatic and meets a Class I recommendation for AVR. In patients without overt symptoms who demonstrate 1) a decrease in systolic BP below baseline or a failure of BP to increase by at least 20 mm Hg or 2) a significant decrease in exercise tolerance compared with age and sex normal standards, symptom onset within 1 to 2 years is high (about 60% to 80%). Thus, it is reasonable to consider elective AVR in these patients when surgical risk is low, taking into account patient preferences and clinical factors such as age and comorbid conditions.

Supporting References: (25, 46, 47, 117, 119-121)

See Online Data Supplement 3 for more information on exercise testing
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIa

3. **AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a (43, 141, 142), *(Level of Evidence: B):***
    a. **Calcified aortic valve with reduced systolic opening;**
    b. **Resting valve area 1.0 cm^2 or less;**
    c. **Aortic velocity less than 4 m per second or mean pressure gradient less than 40 mm Hg;**
    d. **LVEF less than 50%; and**

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e. A low-dose dobutamine stress study that shows an aortic velocity 4 m per second or greater or mean pressure gradient 40 mm Hg or higher with a valve area 1.0 cm^2 or less at any dobutamine dose.

Mean pressure gradient is a strong predictor of outcome after AVR, with better outcomes with higher gradients. Outcomes are poor with severe low-gradient AS but are still improved with AVR compared with medical therapy in those with a low LVEF, particularly when contractile reserve is present. The document "Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice" defines severe AS on dobutamine stress testing as a maximum velocity >4.0 m per second with a valve area ≤1.0 cm^2 at any point during the test protocol, with a maximum dobutamine dose of 20 mcg/kg per minute. On the basis of outcome data in several prospective nonrandomized studies, AVR is reasonable in these patients. LVEF typically increases by 10 LVEF units and may return to normal if afterload mismatch was the cause of LV systolic dysfunction. Some patients without contractile reserve may also benefit from AVR, but decisions in these high-risk patients must be individualized because there are no data indicating who will have a better outcome with surgery.

Supporting References: (43, 99, 137, 141, 142, 151, 152)

See Online Data Supplement 1 for more information on outcomes in patients with low-flow/low-gradient AS with reduced LVEF (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIa

4. AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS (stage D3) with an LVEF 50% or greater, a calcified aortic valve with significantly reduced leaflet motion, and a valve area 1.0 cm^2 or less only if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms and data recorded when the patient is normotensive (systolic BP <140 mm Hg) indicate *(Level of Evidence: C)*:

a. An aortic velocity less than 4 m per second or mean pressure gradient less than 40 mm Hg; and
b. A stroke volume index less than 35 mL/m^2; and
c. An indexed valve area 0.6 cm^2/m^2 or less.

Most patients with severe AS present with a high transvalvular gradient and velocity. However, a subset present with severe AS despite a low gradient and velocity due either to concurrent LV systolic dysfunction (LVEF <50%) or a low transaortic stroke volume with preserved LV systolic function. Studies suggest that low-flow/low-gradient severe AS with preserved LVEF occurs in 5% to 25% of patients with severe AS. Some studies suggest that even asymptomatic patients with low-flow/low-gradient severe AS with a normal LVEF have a poor prognosis and might benefit from AVR. Other studies suggest that many of these asymptomatic patients have only moderate AS with outcomes similar to other patients with moderate AS and normal transaortic flow rates. However, both case control and prospective studies suggest that outcomes are worse in symptomatic patients with low-flow/low-gradient AS with a normal LVEF compared with patients with high-gradient severe AS. Although no RCTs have been done, a post hoc subset analysis of an RCT suggests that

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survival may be improved with TAVR or AVR versus medical management in the symptomatic patient with low-flow severe AS.

The clinical approach to patients with low-flow AS relies on integration of multiple sources of data. Low-flow/low-gradient severe AS with preserved LVEF should be considered in patients with a severely calcified aortic valve, an aortic velocity <4.0 m per second (mean pressure gradient <40 mm Hg), and a valve area ≤1.0 cm^2. However, even with low flow, severe AS is unlikely with a velocity <3.0 m per second or mean pressure gradient <20 mm Hg. Typically, there is a small left ventricle with thick walls, diastolic dysfunction, and a normal LVEF (≥50%). The first diagnostic step is to ensure that data have been recorded and measured correctly. If the patient was hypertensive, repeat evaluation after control of BP should be considered. Next, the valve area should be indexed to body size because an apparent small valve area may be only moderate AS in a small patient; an aortic valve area index ≤0.6 cm^2/m^2 suggests severe AS. Transaortic stroke volume should be calculated from the LV outflow tract diameter and Doppler velocity time integral; a stroke volume indexed to body surface area <35 mL/m^2 is consistent with low flow. If the degree of valve calcification cannot be adequately assessed on TTE, TEE, CT imaging, or fluoroscopy may be considered. The patient should be evaluated for other potential causes of symptoms to ensure that symptoms are most likely due to valve obstruction. The risk of surgery and patient comorbidities should also be taken into account.

Supporting References: (8, 147, 160-167)

See Online Data Supplement 8 for more information on outcomes in patients with low-flow/low-gradient AS with preserved LVEF (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

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Class IIa

5. **AVR is reasonable for patients with moderate AS (stage B) with an aortic velocity between 3.0 m per second and 3.9 m per second or mean pressure gradient between 20 mm Hg and 39 mm Hg who are undergoing cardiac surgery for other indications.** ***(Level of Evidence: C)***

Calcific AS is a progressive disease, and once moderate AS is present, the likelihood of symptom onset within 5 years is significant. When the risk of progressive VHD is balanced against the risk of repeat surgery within 5 years, it is reasonable to perform AVR at the time of other cardiac surgery when moderate AS is present (Sections 4.3.3. and 10). This decision must be individualized based on the specific operative risk in each patient, clinical factors such as age and comorbid conditions, valve durability, and patient preferences.
Supporting References: (25, 92, 138, 155, 156)

Class IIb

1. **AVR may be considered for asymptomatic patients with severe AS (stage C1) with an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher if the patient is at low surgical risk and serial testing shows an increase in aortic velocity 0.3 m per second or greater per year.** ***(Level of Evidence: C)***

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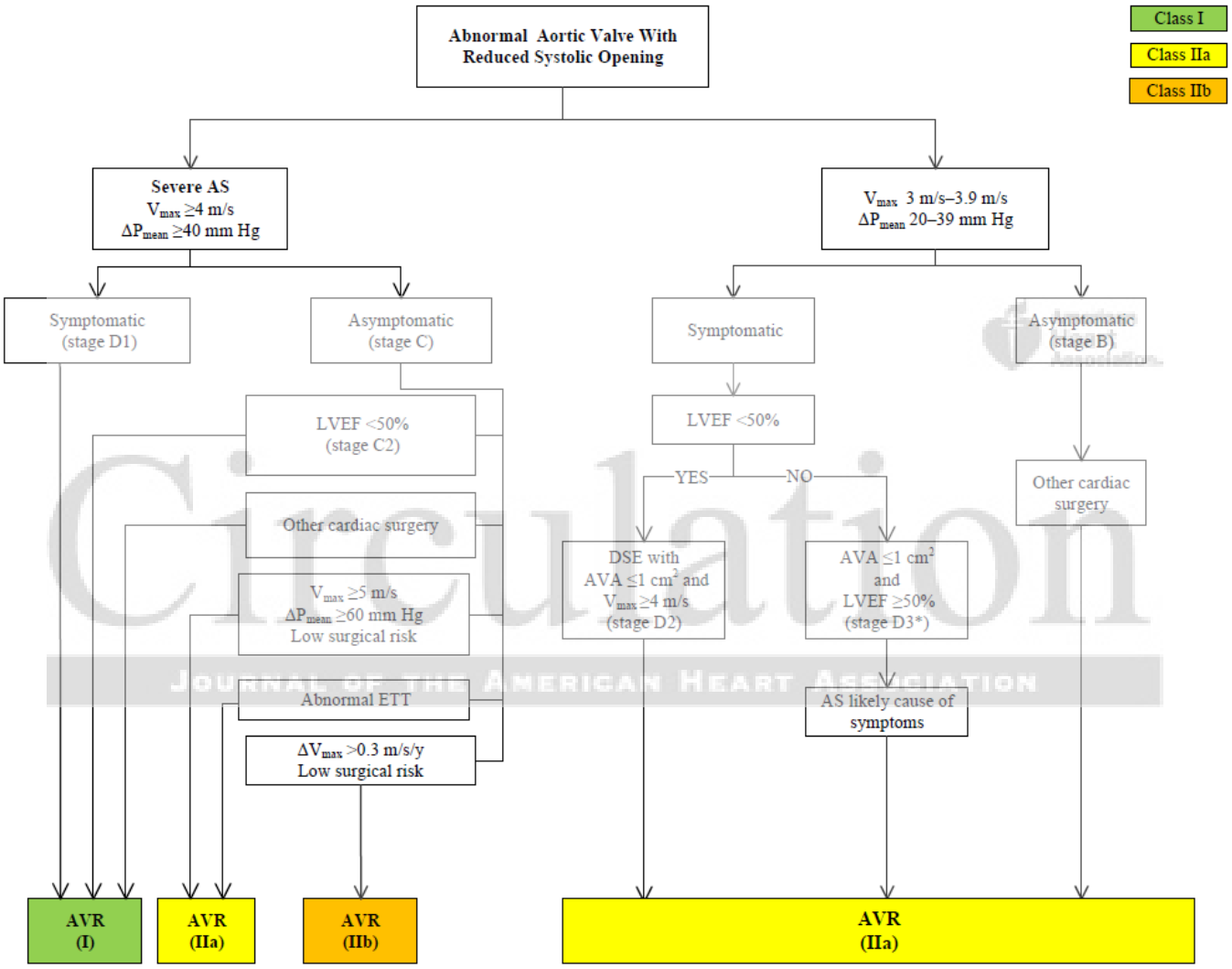
Predictors of rapid disease progression include older age, more severe valve calcification, and a faster rate of hemodynamic progression on serial studies. In patients with severe AS and predictors of rapid disease progression, elective AVR may be considered if the surgical risk is low and after consideration of other clinical factors and patient preferences.

Supporting References: (115, 168, 169)

Figure 1. Indications for AVR in Patients With AS



Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention.
*AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 mL/m^2, indexed AVA is ≤0.6 cm^2/m^2, and data are recorded when the patient is normotensive (systolic BP <140 mm Hg).
AS indicates aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; and V_{max}, maximum velocity.

3.2.4. Choice of Intervention: Recommendation

See Table 10 for a summary of recommendations from this section.

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These recommendations for choice of intervention for AS apply to both surgical and transcatheter AVR; indications for AVR are discussed in Section 3.2.3. The integrative approach to assessing risk of surgical or transcatheter AVR is discussed in Section 2.5. The choice of proceeding with surgical versus transcatheter AVR is based on multiple parameters, including the risk of operation, patient frailty, and comorbid conditions. Concomitant severe CAD may also affect the optimal intervention, because severe multivessel coronary disease may best be served by AVR and CABG.

Table 10. Summary of Recommendations for AS: Choice of Surgical or Transcatheter Intervention

Recommendations	COR	LOE	References
Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.2.3) with low or intermediate surgical risk	I	A	(74, 149)
For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care	I	C	N/A
TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 mo	I	B	(170, 171)
TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.2.3) and who have high surgical risk (Section 2.5)	IIa	B	(172, 173)
Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS	IIb	C	N/A
TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS	III: No Benefit	B	(170)

AS indicates aortic stenosis; AVR, aortic valve replacement; COR, Class of Recommendation; LOE, Level of Evidence; N/A, not applicable; and TAVR, transcatheter aortic valve replacement.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Class I

1. **Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.2.3) with low or intermediate surgical risk (Section 2.5) (74, 149). *(Level of Evidence: A)***

AVR is indicated for survival benefit, improvement in symptoms, and improvement in LV systolic function in patients with severe symptomatic AS (Section 3.2.3). Given the magnitude of the difference in outcomes between those undergoing AVR and those who refuse AVR in historical series, an RCT of AVR versus medical therapy would not be appropriate in patients with a low to intermediate surgical risk (Section 2.5). Outcomes after surgical AVR are excellent in patients who do not have a high procedural risk. Surgical series demonstrate improved symptoms after AVR, and most patients have an improvement in exercise tolerance as documented in studies with pre- and post-AVR exercise stress testing. The specific choice of prosthetic valve type is discussed in Section 11.1. Surgical AVR should be considered over TAVR in patients who are at higher surgical risk but have severe multivessel coronary disease.

Supporting References: (74, 93, 174-177)

Class I

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2. **For patients in whom TAVR or high-risk surgical AVR is being considered, a Heart Valve Team consisting of an integrated, multidisciplinary group of healthcare professionals with expertise in VHD, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery should collaborate to provide optimal patient care. *(Level of Evidence: C)***

Decision making is complex in the patient at high surgical risk with severe symptomatic AS. The decision to perform surgical AVR, TAVR, or to forgo intervention requires input from a Heart Valve Team. The primary cardiologist is aware of coexisting conditions that affect risk and long-term survival, the patient's disease course, and the patient's preferences and values. Cardiac imaging specialists who are knowledgeable about AS and TAVR provide evaluation of aortic valve anatomy and hemodynamic severity, vascular anatomy, aortic annulus size, and coronary anatomy, including the annular-ostial distance. Interventional cardiologists help determine the likelihood of a successful transcatheter procedure. The cardiac surgeon can provide a realistic estimate of risk with a conventional surgical approach, at times in conjunction with a cardiac anesthesiologist. An expert in VHD, typically a cardiologist or cardiac surgeon with expertise in imaging and/or intervention, provides the continuity and integration needed for the collaborative decision-making process. Nurses and other members of the team coordinate care and help with patient education. The cardiac surgeon and interventional cardiologist are the core of the Heart Valve Team for patients being considered for AVR or TAVR.
Supporting References: (79, 178)

Class I

3. **TAVR is recommended in patients who meet an indication for AVR (Section 3.2.3) who have a prohibitive risk for surgical AVR (Section 2.5) and a predicted post-TAVR survival greater than 12 months (170, 171). *(Level of Evidence: B)***

TAVR has been studied in numerous observational studies and multicenter registries that include large numbers of high-risk patients with severe symptomatic AS. These studies demonstrated the feasibility, excellent hemodynamic results, and favorable outcomes with the procedure. In addition, TAVR was compared with standard therapy in a prospective RCT of patients with severe symptomatic AS who were deemed inoperable. Severe AS was defined as an aortic valve area <0.8 cm^2 plus a mean pressure gradient ≥40 mm Hg or a maximum aortic velocity ≥4.0 m per second. All patients had NYHA class II to IV symptoms. Patients were considered to have a prohibitive surgical risk when predicted 30-day surgical morbidity and mortality was ≥50% due to comorbid disease or a serious irreversible condition. Patients were excluded if they had a bicuspid aortic valve, acute myocardial infarction (MI), significant CAD, an LVEF <20%, an aortic annulus diameter <18 mm or >25 mm, severe AR or MR, a transient ischemic attack within 6 months, or severe renal insufficiency. TAVR was performed by either the transfemoral or transapical approach using the SAPIEN heart-valve system (Edwards Lifesciences LLC, Irvine, CA). Standard therapy included percutaneous aortic balloon dilation in 84%.

All-cause death at 2 years was lower with TAVR (43.3%) compared with standard medical therapy (68%), with an HR for TAVR of 0.58 (95% CI: 0.36 to 0.92; p=0.02). There was a reduction in repeat

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hospitalization with TAVR (55% versus 72.5%; p<0.001). In addition, only 25.2% of survivors were in NYHA class III or IV 1 year after TAVR, compared with 58% of patients receiving standard therapy (p<0.001). However, the rate of major stroke at 30 days was higher with TAVR (5.05% versus 1.0%; p=0.06) and remained higher at 2 years with TAVR compared with standard therapy (13.8% versus 5.5%; p=0.01). Major vascular complications occurred in 16.2% with TAVR versus 1.1% with standard therapy (p<0.001).

Thus, in high-risk patients with severe symptomatic AS who are unable to undergo surgical AVR due to a prohibitive surgical risk and who have an expected survival of >1 year after intervention, TAVR is recommended to improve survival and reduce symptoms. This decision should be made only after discussion with the patient about the expected benefits and possible complications of TAVR and surgical AVR. Patients with severe AS are considered to have a prohibitive surgical risk if they have a predicted risk with surgery of death or major morbidity (all cause) of >50% at 1 year; disease affecting ≥3 major organ systems that is not likely to improve postoperatively; or anatomic factors that preclude or increase the risk of cardiac surgery, such as a heavily calcified (e.g., porcelain) aorta, prior radiation, or an arterial bypass graft adherent to the chest wall.
Supporting References: (170, 171, 179)

Class IIa

1. **TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.2.3) and who have high surgical risk for surgical AVR (Section 2.5) (172, 173). *(Level of Evidence: B)***

TAVR has been studied in numerous observational studies and multicenter registries that include large numbers of high-risk patients with severe symptomatic AS. These studies demonstrated the feasibility, excellent hemodynamic results, and favorable outcomes with the procedure. In addition, TAVR was compared with standard therapy in a prospective RCT of patients with severe symptomatic AS who were deemed high risk for surgery. Severe symptomatic calcific AS was defined as aortic valve area <0.8 cm^2 plus a mean transaortic gradient ≥40 mm Hg or aortic velocity ≥4.0 m per second with NYHA class II to IV symptoms. Patients were deemed at high surgical risk if risk of death was ≥15% within 30 days after the procedure. An STS score ≥10% was used for guidance, with an actual mean STS score of 11.8±3.3%. Exclusions included bicuspid aortic valve anatomy, acute MI, significant CAD, an LVEF <20%, an aortic annulus diameter <18 mm or >25 mm, severe AR or MR, transient ischemic attack within 6 months, or severe renal insufficiency. On an intention-to-treat analysis, all-cause death was similar in those randomized to TAVR (n=348) compared with surgical AVR (n=351) at 30 days, 1 year, and 2 years (p=0.001) for noninferiority of TAVR compared with surgical AVR. The composite endpoint of all-cause death or stroke at 2 years was 35% with surgical AVR compared with 33.9% with TAVR (p=0.78). TAVR was performed by the transfemoral approach in 244 patients and the transapical approach in 104 patients. Only limited data on long-term durability of bioprosthetic valves implanted by the transcatheter approach are available.

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Given the known long-term outcomes and valve durability with surgical AVR, TAVR currently remains restricted to patients with prohibitive or high surgical risk. High surgical risk is defined as an STS PROM score of 8% to 15%, anatomic factors that increase surgical risk, or significant frailty (Section 14.2).
Supporting References: (172, 173, 180, 181)

See Online Data Supplement 9 for more information on choice of intervention
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIb

1. **Percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or TAVR in patients with severe symptomatic AS.** ***(Level of Evidence: C)***

Percutaneous aortic balloon dilation has an important role in treating children, adolescents, and young adults with AS, but its role in treating older patients is very limited. The mechanism by which balloon dilation modestly reduces the severity of stenosis in older patients is by fracture of calcific deposits within the valve leaflets and, to a minor degree, stretching of the annulus and separation of the calcified or fused commissures. Immediate hemodynamic results include a moderate reduction in the transvalvular pressure gradient, but the postdilation valve area rarely exceeds 1.0 cm^2. Despite the modest change in valve area, an early symptomatic improvement usually occurs. However, serious acute complications, including acute severe AR and restenosis and clinical deterioration, occur within 6 to 12 months in most patients. Therefore, in patients with AS, percutaneous aortic balloon dilation is not a substitute for AVR.

Some clinicians contend that despite the procedural morbidity and mortality and limited long-term results, percutaneous aortic balloon dilation can have a temporary role in the management of some symptomatic patients who are not initially candidates for surgical AVR or TAVR. For example, patients with severe AS and refractory pulmonary edema or cardiogenic shock might benefit from percutaneous aortic balloon dilation as a "bridge" to AVR; an improved hemodynamic state may reduce the risks of TAVR or surgery. In some patients, the effects of percutaneous aortic balloon dilation on symptoms and LV function may be diagnostically helpful as well, but many clinicians recommend proceeding directly to AVR in these cases. The indications for palliative percutaneous aortic balloon dilation in patients in whom AVR cannot be recommended because of serious comorbid conditions are even less well established, with no data to suggest improved longevity; however, some patients do report a decrease in symptoms. Most asymptomatic patients with severe AS who require urgent noncardiac surgery can undergo surgery at a reasonably low risk with anesthetic monitoring and attention to fluid balance. Percutaneous aortic balloon dilation is not recommended for these patients. If preoperative correction of AS is needed, they should be considered for AVR.
Supporting References: (172, 173, 182-184)

Class III: No Benefit

1. **TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (170).** ***(Level of Evidence: B)***

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The survival and symptom reduction benefit of TAVR is only seen in appropriately selected patients. Baseline clinical factors associated with a poor outcome after TAVR include advanced age, frailty, smoking or chronic obstructive pulmonary disease, pulmonary hypertension, liver disease, prior stroke, anemia, and other systemic conditions. The STS estimated surgical risk score provides a useful measure of the extent of patient comorbidities and may help identify which patients will benefit from TAVR. In patients with a prohibitive surgical risk for AVR in the PARTNER (Placement of Aortic Transcatheter Valve) study, the survival benefit of TAVR was seen in those with an STS score <5% (n=40, HR: 0.37; 95% CI: 0.13 to 1.01; p=0.04) and in those with an STS score between 5% and 14.9% (n=227, HR: 0.58; 95% CI: 0.41 to 0.8; p=0.002) but not in those with an STS score ≥15% (n=90, HR: 0.77; 95% CI: 0.46 to 1.28; p=0.31). The relative prevalence of oxygen-dependent lung disease was similar in all 3 groups. However, the other reasons for inoperability were quite different, with a porcelain aorta or prior chest radiation damage being most common in those with an STS score of <5% and frailty being most common in those with an STS score ≥15%. These data emphasize the importance of evaluating the likely benefit of TAVR, as well as the risks, in weighing the risk–benefit ratio of intervention in an individual patient. TAVR is not recommended in patients with 1) a life expectancy of <1 year, even with a successful procedure, and 2) those with a chance of "survival with benefit" of <25% at 2 years.

Supporting References: (115, 170, 179, 185)

4. Aortic Regurgitation

4.1. Acute AR

Acute AR may result from abnormalities of the valve, primarily IE, or abnormalities of the aorta, primarily aortic dissection. Acute AR may also occur from iatrogenic complications, such as following percutaneous aortic balloon dilation or TAVR or following blunt chest trauma. The acute volume overload on the left ventricle usually results in severe pulmonary congestion as well as a low forward cardiac output. Urgent diagnosis and rapid intervention can be lifesaving.

4.1.1. Diagnosis

TTE is indispensable in confirming the presence, severity, and etiology of AR, estimating the degree of pulmonary hypertension, and determining whether there is rapid equilibration of aortic and LV diastolic pressure. Short deceleration time on the mitral flow velocity curve and early closure of the mitral valve on M-mode echocardiography are indicators of markedly elevated LV end-diastolic pressure. A short half-time of <300 milliseconds on the AR velocity curve indicates rapid equilibration of the aortic and LV diastolic pressures. Assessing reversed flow during diastole in the aortic arch in comparison with the forward systolic flow provides a quick semiquantitative estimate of regurgitant fraction.

Acute severe AR caused by aortic dissection is a surgical emergency that requires particularly prompt identification and management. However, the presence of new, even mild, AR, diagnosed by auscultation of a diastolic murmur or findings on echocardiography, may be a sign of acute aortic dissection. The sensitivity and

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specificity of TTE for diagnosis of aortic dissection are only 60% to 80%, whereas TEE has a sensitivity of 98% to 100% and a specificity of 95% to 100%. CT imaging is also very accurate and may provide the most rapid approach to diagnosis at many centers. CMR imaging is useful with chronic aortic disease but is rarely used in unstable patients with suspected dissection. Angiography should be considered only when the diagnosis cannot be determined by noninvasive imaging and when patients have suspected or known CAD, especially those with previous CABG.

4.1.2. Intervention

In patients with acute severe AR resulting from IE or aortic dissection, surgery should not be delayed, especially if there is hypotension, pulmonary edema, or evidence of low flow (Section 12). Numerous studies have demonstrated improved in-hospital and long-term survival in such patients if they are treated with prompt AVR, as long as there are no complications (such as severe embolic cerebral damage) or comorbid conditions that make the prospect of recovery remote. In a prospectively enrolled multinational cohort of 1,552 patients with definite native valve endocarditis (NVE), evidence of new AR was present in 37% of patients. HF (HR: 2.33; 95% CI: 1.65 to 3.28; p<0.001) and pulmonary edema (HR: 1.51; 95% CI: 1.04 to 2.18; p=0.029) were associated with increased in-hospital mortality. Early surgery was associated with reduced in-hospital mortality (HR: 0.56, 95% CI: 0.38 to 0.82; p=0.003). The effect of early surgery on in-hospital mortality was also assessed by propensity-based matching adjustment for survivor bias and by instrumental variable analysis. Compared with medical therapy, early surgery in the propensity-matched cohort after adjustment for survivor bias was associated with an absolute risk reduction of 5.9% (p<0.001) for in-hospital mortality.

Intra-aortic balloon counterpulsation is contraindicated in patients with acute severe AR. Augmentation of aortic diastolic pressure will worsen the severity of the acute regurgitant volume, thereby aggravating LV filling pressures and compromising forward output.

Beta blockers are often used in treating aortic dissection. However, these agents should be used very cautiously, if at all, for other causes of acute AR because they will block the compensatory tachycardia and could precipitate a marked reduction in BP.

Supporting References: (186-196)

4.2. Stages of Chronic AR

The most common causes of chronic AR in the United States and other developed countries are bicuspid aortic valve and calcific valve disease. In addition, AR frequently arises from primary diseases causing dilation of the ascending aorta or the sinuses of Valsalva. Another cause of AR is rheumatic heart disease (the leading cause in many developing countries). In the majority of patients with AR, the disease course is chronic and slowly progressive with increasing LV volume overload and LV adaptation via chamber dilation and hypertrophy. Management of patients with AR depends on accurate diagnosis of the cause and stage of the disease process. Table 11 shows the stages of AR ranging from patients at risk of AR (stage A) or with progressive mild-to-moderate AR (stage B) to severe asymptomatic (stage C) and symptomatic AR (stage D). Each of these stages is

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defined by valve anatomy, valve hemodynamics, severity of LV dilation, and LV systolic function, as well as by patient symptoms.

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Table 11. Stages of Chronic AR

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk of AR**	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis • Diseases of the aortic sinuses or ascending aorta • History of rheumatic fever or known rheumatic heart disease • IE	• AR severity: none or trace	• None	• None
B	**Progressive AR**	• Mild-to-moderate calcification of a trileaflet valve bicuspid aortic valve (or other congenital valve anomaly) • Dilated aortic sinuses • Rheumatic valve changes • Previous IE	• **Mild AR:** o Jet width <25% of LVOT; o Vena contracta <0.3 cm; o RVol <30 mL/beat; o RF <30%; o ERO <0.10 cm^2; o Angiography grade 1+ • **Moderate AR:** o Jet width 25%–64% of LVOT; o Vena contracta 0.3–0.6 cm; o RVol 30–59 mL/beat; o RF 30%–49%; o ERO 0.10–0.29 cm^2; o Angiography grade 2+	• Normal LV systolic function • Normal LV volume or mild LV dilation	• None
C	**Asymptomatic severe AR**	• Calcific aortic valve disease • Bicuspid valve (or other congenital abnormality) • Dilated aortic sinuses or ascending aorta • Rheumatic valve changes • IE with abnormal leaflet closure or perforation	• **Severe AR:** o Jet width ≥65% of LVOT; o Vena contracta >0.6 cm; o Holodiastolic flow reversal in the proximal abdominal aorta o RVol ≥60 mL/beat; o RF ≥50%; o ERO ≥0.3 cm^2; o Angiography grade 3+ to 4+; o In addition, diagnosis of chronic severe AR requires evidence of LV dilation	**C1:** Normal LVEF (≥50%) and mild-to-moderate LV dilation (LVESD ≤50 mm) **C2:** Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilatation (LVESD >50 mm or indexed LVESD >25 mm/m^2)	• None; exercise testing is reasonable to confirm symptom status

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D	**Symptomatic severe AR**	• Calcific valve disease • Bicuspid valve (or other congenital abnormality) • Dilated aortic sinuses or ascending aorta • Rheumatic valve changes • Previous IE with abnormal leaflet closure or perforation	• **Severe AR:** o Doppler jet width ≥65% of LVOT; o Vena contracta >0.6 cm, o Holodiastolic flow reversal in the proximal abdominal aorta, o RVol ≥60 mL/beat; o RF ≥50%; o ERO ≥0.3 cm^2; o Angiography grade 3+ to 4+ o In addition, diagnosis of chronic severe AR requires evidence of LV dilation	• Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%), mild-to-moderate LV dysfunction (LVEF 40% to 50%), or severe LV dysfunction (LVEF <40%); • Moderate-to-severe LV dilation is present.	• Exertional dyspnea or angina or more severe HF symptoms

AR indicates aortic regurgitation; ERO, effective regurgitant orifice; HF, heart failure; IE, infective endocarditis; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVOT, left ventricular outflow tract; RF, regurgitant fraction; and RVol, regurgitant volume.

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4.3. Chronic AR

See Figure 2 for indications for AVR for chronic AR.

4.3.1. Diagnosis and Follow-Up

4.3.1.1. Diagnostic Testing—Initial Diagnosis: Recommendations

Class I

1. **TTE is indicated in patients with signs or symptoms of AR (stages A to D) for accurate diagnosis of the cause of regurgitation, regurgitant severity, and LV size and systolic function, and for determining clinical outcome and timing of valve intervention (32, 197-206). *(Level of Evidence: B)***

The clinical stages that characterize the severity of chronic AR (Table 11) are defined by symptomatic status, severity of regurgitation, and LV volume and systolic function. TTE is an indispensable imaging test for evaluating patients with chronic AR and guiding appropriate management decisions. It provides diagnostic information about the etiology and mechanism of AR (including valve reparability), severity of regurgitation, morphology of the ascending aorta, and LV response to the increases in preload and afterload. Quantitative measures of regurgitant volume and effective regurgitant orifice area were strong predictors of clinical outcome in a prospective study of 251 asymptomatic patients with isolated AR and normal LV function (stages B and C). This was confirmed in a subsequent study involving 294 patients. Observation of diastolic flow reversal in the aortic arch or more distally can help identify patients with severe AR. Numerous studies involving a total of >1,150 patients have consistently shown that measures of LV systolic function (LVEF or fractional shortening) and LV end-systolic dimension (LVESD) or volume are associated with development of HF symptoms or death in initially asymptomatic patients (stages B and C1). Moreover, in symptomatic patients undergoing AVR (stage D), preoperative LV systolic function and end-systolic dimension or volume are significant determinants of survival and functional results after surgery. Symptomatic patients (stage D) with normal LVEF have significantly better long-term postoperative survival than those with depressed systolic function.
Supporting References: (17, 32, 197-221)

See Online Data Supplement 10 for more information on the natural history of asymptomatic AR
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

2. **TTE is indicated in patients with dilated aortic sinuses or ascending aorta or with a bicuspid aortic valve (stages A and B) to evaluate the presence and severity of AR (222). *(Level of Evidence: B)***

A diastolic regurgitant murmur is not always audible in patients with mild or moderate AR. TTE is more sensitive than auscultation in detecting AR in patients at risk for development of AR. In a series of 100 patients referred for echocardiographic evaluation of a systolic murmur, 28 had AR on echocardiography. Auscultation had high specificity (96%) for detecting AR but low sensitivity (21%), and diagnostic accuracy was only 75%.
Supporting Reference: (222)

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Class I

3. **CMR is indicated in patients with moderate or severe AR (stages B, C, and D) and suboptimal echocardiographic images for the assessment of LV systolic function, systolic and diastolic volumes, and measurement of AR severity (223, 224).** ***(Level of Evidence: B)***

CMR imaging provides accurate measures of regurgitant volume and regurgitant fraction in patients with AR, as well as assessment of aortic morphology, LV volume, and LV systolic function. In addition to its value in patients with suboptimal echocardiographic data, CMR is useful for evaluating patients in whom there is discordance between clinical assessment and severity of AR by echocardiography. CMR measurement of regurgitant severity is less variable than echocardiographic measurement.

Supporting References: (223-229)

4.3.1.2. Diagnostic Testing—Changing Signs or Symptoms

Symptoms are the most common indication for AVR in patients with AR. In patients with previous documentation of mild or moderate AR, new-onset dyspnea or angina may indicate that AR has progressed in severity. If AR remains mild, further investigation for other etiologies is indicated. In patients with previous documentation of severe AR, onset of symptoms is an indication for surgery and repeat TTE is indicated to determine the status of the aortic valve, aorta, and left ventricle preoperatively.

Supporting References: (31, 215, 221, 230, 231)

4.3.1.3. Diagnostic Testing—Routine Follow-Up

Patients with asymptomatic severe AR with normal LV systolic function are at risk for progressive increases in LV end-diastolic and end-systolic volumes and reduction in systolic function. In a series of asymptomatic patients with AR and normal LV systolic function who underwent serial echocardiograms, predictors of death or symptoms in a multivariate analysis were age, initial end-systolic dimension, and rate of change in end-systolic dimension and rest LVEF during serial studies. In asymptomatic patients who do not fulfill the criteria for AVR, serial imaging is indicated to identify those who are progressing toward the threshold for surgery (Table 4).

Supporting Reference: (32)

4.3.1.4. Diagnostic Testing—Cardiac Catheterization

When there is discordance between clinical assessment and noninvasive tests about the severity of AR, additional testing is indicated. Under most circumstances, another noninvasive test such as CMR is used when TTE and clinical findings are discordant. Invasive assessment is indicated when CMR is not available or there are contraindications for CMR, such as implanted devices. In symptomatic patients with equivocal echocardiographic evidence of severity of AR, cardiac catheterization is useful to assess hemodynamics, coronary artery anatomy, and severity of AR.

Supporting References: (223, 225-229)

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4.3.1.5. Diagnostic Testing—Exercise Testing

Exercise stress testing can be used to assess symptomatic status and functional capacity in patients with AR. Such testing is helpful in confirming patients' reports that they have no symptoms with daily life activities and in assessing objective exercise capacity and symptom status in those with equivocal symptoms.

4.3.2. Medical Therapy: Recommendations

Class I

1. **Treatment of hypertension (systolic BP >140 mm Hg) is recommended in patients with chronic AR (stages B and C), preferably with dihydropyridine calcium channel blockers or ACE inhibitors/ARBs (205, 210). *(Level of Evidence: B)***

Vasodilating drugs are effective in reducing systolic BP in patients with chronic AR. Beta blockers may be less effective because the reduction in heart rate is associated with an even higher stroke volume, which contributes to the elevated systolic pressure in patients with chronic severe AR.

Supporting References: (205, 210, 232-234)

Class IIa

1. **Medical therapy with ACE inhibitors/ARBs and beta blockers is reasonable in patients with severe AR who have symptoms and/or LV dysfunction (stages C2 and D) when surgery is not performed because of comorbidities (233, 235). (*Level of Evidence: B*)**

Vasodilating drugs improve hemodynamic abnormalities in patients with AR and improve forward cardiac output. However, 2 small RCTs yielding discordant results did not conclusively show that these drugs alter the natural history of asymptomatic patients with chronic severe AR and normal LV systolic function. Thus, vasodilator therapy is not recommended routinely in patients with chronic asymptomatic AR and normal LV systolic function.

In symptomatic patients who are candidates for surgery, medical therapy is not a substitute for AVR. However, medical therapy is helpful for alleviating symptoms in patients who are considered at very high risk for surgery because of concomitant comorbid medical conditions. In a cohort study of 2,266 patients with chronic AR, treatment with ACE inhibitors or ARBs was associated with a reduced composite endpoint of AVR, hospitalization for HF, and death from HF (HR: 0.68; 95% CI: 0.54 to 0.87; p<0.01). In that study, 45% had evidence of LV systolic impairment. In another retrospective cohort study of 756 patients with chronic AR, therapy with beta-adrenergic blockers was associated with improved survival (HR: 0.74; 95% CI: 0.58 to 0.93; p<0.01). Also, 33% of patients had associated CAD, 64% had hypertension, 20% had renal insufficiency, 70% had HF, and 25% had AF. Patients treated with beta blockers were more likely to also be taking ACE inhibitors (53% versus 40%; p<0.001) and dihydropyridine calcium channel blockers (22% versus 16%; p=0.03). Importantly, more patients receiving beta blockers in that study underwent AVR (49% versus 29%; p<0.001), but this was accounted for in the multivariate model. When patients were censored at the time of surgery, beta-blocker therapy remained associated with higher survival rates (p<0.05).

Supporting References: (205, 210, 232, 233, 235-240)

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See Online Data Supplement 11 for more information on vasodilator therapy in AR (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

4.3.3. Timing of Intervention: Recommendations

See Table 12 for a summary of recommendations from this section.

Table 12. Summary of Recommendations for AR Intervention

Recommendations	COR	LOE	References
AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D)	I	B	(31, 230, 231)
AVR is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%) (stage C2)	I	B	(212, 230, 241, 242)
AVR is indicated for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications	I	C	N/A
AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%) but with severe LV dilation (LVESD >50 mm, stage C2)	IIa	B	(226, 243, 244)
AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery	IIa	C	N/A
AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function (LVEF ≥50%, stage C1) but with progressive severe LV dilation (LVEDD >65 mm) if surgical risk is low*	IIb	C	N/A

*Particularly in the setting of progressive LV enlargement.

AR indicates aortic regurgitation; AVR, aortic valve replacement; COR, Class of Recommendation; LOE, Level of Evidence; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; and N/A, not applicable.

The vast majority of patients who require surgery for chronic severe AR will require AVR. Valve-sparing replacement of the aortic sinuses and ascending aorta is a possible strategy in patients with AR caused by aortic dilation in whom a trileaflet or bicuspid valve is not thickened, deformed, or calcified. Despite advances in primary aortic valve repair, especially in young patients with bicuspid aortic valves, the experience at a few specialized centers has not yet been replicated at the general community level, and durability of aortic valve repair remains a major concern. Performance of aortic valve repair should be concentrated in those centers with proven expertise in the procedure.

Supporting References: (245-248)

Class I

1. **AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D) (31, 230, 231). *(Level of Evidence: B)***

Symptoms are an important indication for AVR in patients with chronic severe AR, and the most important aspect of the clinical evaluation is taking a careful, detailed history to elicit symptoms or diminution of exercise capacity. Patients with chronic severe AR who develop symptoms have a high risk of death if AVR is not performed. In a series of 246 patients with severe AR followed without surgery, those who were NYHA class III or IV had a mortality rate of 24.6% per year; even NYHA class II symptoms were associated with increased mortality (6.3% per year). Numerous other studies indicate that survival and functional status after AVR are

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related to severity of preoperative symptoms assessed either subjectively or objectively with exercise testing, with worse outcomes in patients who undergo surgery after development of moderately severe (NYHA class III) symptoms or impaired exercise capacity. In a series of 289 patients followed after AVR, long-term postoperative survival was significantly higher in patients who were in NYHA class I or II at the time of surgery compared with those in NYHA class III or IV (10-year survival rates 78±7% versus 45±4%, respectively; p<0.001). The importance of preoperative symptoms in the study was observed for both patients with normal LV systolic function and those with LV systolic dysfunction. Postoperative survival is significantly higher in symptomatic patients with normal LVEF compared with those with impaired systolic function, but even in symptomatic patients with severely depressed systolic function, surgery is recommended over medical therapy. In a postoperative series of 450 patients undergoing AVR from 1980 to 1995, patients with markedly low LVEF incurred high short- and long-term mortality after AVR. However, postoperative LV function improved significantly, and most patients survived without recurrence of HF. This was confirmed in a series of 724 patients who underwent AVR from 1972 to 1999, in which long-term survival was significantly reduced in the 88 patients with severe LV dysfunction (LVEF <30%) compared with the 636 patients with either less severe LV dysfunction or normal LVEF (81% versus 92% at 1 year, 68% versus 81% at 5 years, 46% versus 62% at 10 years, 26% versus 41% at 15 years, and 12% versus 24% at 20 years, respectively; p=0.04). Among propensity-matched patients operated on in the latter time frame since 1985, these trends were no longer significant (survival at 1, 5, and 10 years after surgery was 92%, 79%, and 51% for patients with severe LV dysfunction and 96%, 83%, and 55% for the others, respectively; p=0.9).

Supporting References: (31, 212-222, 230, 231, 241, 242, 249, 250)

See Online Data Supplement 12 for more information on outcome after surgery for AR (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

2. **AVR is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%) at rest (stage C2) if no other cause for systolic dysfunction is identified (212, 230, 241, 242). *(Level of Evidence: B)***

After AVR, LV systolic function is an important determinant of survival and functional status for chronic severe AR. Optimal outcomes are obtained when surgery is performed before LVEF decreases below 50%. However, among patients with LV systolic dysfunction, LV function will improve in many after surgery, especially those with minimal or no symptoms, mild versus severe LV systolic dysfunction, and a brief duration of LV dysfunction. A series of 37 patients with severe AR who underwent AVR were studied, all of whom had preoperative LV dysfunction but preserved exercise capacity (including 8 asymptomatic patients). In the 10 patients in whom LV dysfunction had developed <14 months preoperatively, there was a greater improvement in LV systolic function and regression of LV dilatation compared with those patients who had a longer duration of LV dysfunction. Patients with preserved exercise capacity had higher survival rates, a shorter duration of LV dysfunction, and a persistent improvement in LV size and systolic function at late postoperative studies at 3 to 7

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years. Thus, once LV systolic dysfunction (LVEF <50%) is demonstrated, results are optimized by referring for surgery rather than waiting for onset of symptoms or more severe LV dysfunction.

Supporting References: (17, 212-221, 230, 241-243, 250, 251)

Class I

3. **AVR is indicated for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications. *(Level of Evidence: C)***

Patients with chronic severe AR should undergo AVR if they are referred for other forms of cardiac surgery, such as CABG, mitral valve surgery, or replacement of the ascending aorta. This will prevent both the hemodynamic consequences of persistent AR during the perioperative period and the possible need for a second cardiac operation in the near future.

Class IIa

1. **AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%) but with severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2) (stage C2) (226, 243, 244). *(Level of Evidence: B)***

LVESD in patients with chronic AR reflects both the severity of the LV volume overload and the degree of LV systolic shortening. An elevated end-systolic dimension often reflects LV systolic dysfunction with a depressed LVEF. If LVEF is normal, an increased LVESD indicates a significant degree of LV remodeling and is associated with subsequent development of symptoms and/or LV systolic dysfunction. In a series of 104 initially asymptomatic patients with normal LV systolic function followed for a mean of 8 years, an LVESD >50 mm was associated with a risk of death, symptoms, and/or LV dysfunction of 19% per year. In a second study of 101 similar patients followed for a mean of 5 years, this risk was 7% per year. In a third study of 75 similar patients followed for a mean of 10 years, the risk was 7.6% per year. Among patients undergoing AVR, a smaller LVESD is associated with both better survival and improvement in LV systolic function after surgery. Most studies used unadjusted LV dimension, with more recent data suggesting that indexing for body size may be appropriate, particularly in women or small patients. A study of 246 patients that adjusted end-systolic dimension for body size suggested that an end-systolic dimension ≥25 mm/m^2 is associated with a poor outcome in asymptomatic patients. This has been confirmed by a subsequent study of 294 asymptomatic patients in which an end-systolic dimension >24 mm/m^2 was an independent predictor of LV systolic dysfunction, symptoms, or death, and an earlier study of 32 patients in which an end-systolic dimension >26 mm/m^2 was associated with persistent LV dilation after AVR. Other studies have suggested that end-systolic volume index is a more sensitive predictor of cardiac events than end-systolic dimension in asymptomatic patients, but values of end-systolic volume index identifying high-risk patients have varied between 35 mL/m^2 and 45 mL/m^2 in 2 studies. Thus, more data are needed to determine threshold values of end-systolic volume index with which to make recommendations for surgery in asymptomatic patients.

Supporting References: (17, 31, 32, 197, 198, 200, 204-206, 209, 213-217, 219, 243, 244, 250, 252-255)

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See Online Data Supplement 12 for more information on AVR in asymptomatic patients (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIa

2. **AVR is reasonable in patients with moderate AR (stage B) while undergoing surgery on the ascending aorta, CABG, or mitral valve surgery. *(Level of Evidence: C)***

Because of the likelihood of progression of AR and the need for future AVR in patients with moderate AR, it is reasonable to replace the aortic valve in patients who have evidence of primary aortic valve leaflet disease or significant aortic dilation if they are referred for other forms of cardiac surgery, such as CABG, mitral valve surgery, or replacement of the ascending aorta.

Class IIb

1. **AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function at rest (LVEF ≥50%, stage C1) but with progressive severe LV dilatation (LV end-diastolic dimension >65 mm) if surgical risk is low. *(Level of Evidence: C)***

LV end-diastolic dimension is indicative of the severity of LV volume overload in patients with chronic AR. It is significantly associated with development of symptoms and/or LV systolic dysfunction in asymptomatic patients but less so than LVESD. Similarly, end-diastolic volume index is less predictive than end-systolic volume index in asymptomatic patients. However, especially in young patients with severe AR, progressive increases in end-diastolic dimension are associated with a subsequent need for surgery. In a series of 104 initially asymptomatic patients with normal LV systolic function followed for a mean of 8 years, an LV end-diastolic dimension of ≥70 mm was associated with a risk of death, symptoms, and/or LV dysfunction of 10% per year. In a second study of 101 patients followed for a mean of 5 years, this risk was 6.3% per year; in a third study of 75 patients followed for a mean of 10 years, the risk was 5.8% per year. Marked increases in end-diastolic dimension (≥80 mm) have been associated with sudden death. The writing committee thought that AVR may be considered for the asymptomatic patient with severe AR, normal LV systolic function, and severe LV dilatation (LV end-diastolic dimension >65 mm) if there is a low surgical risk and particularly if there is evidence of progressive LV dilation.

New markers of severity of AR and its resultant LV volume overload are under investigation. These include measures of regurgitant fraction, regurgitant volume, and effective regurgitant orifice area; LV volume assessment with 3D echocardiography; noninvasive measures of LV end-systolic stress and systolic and diastolic strain rates; and biomarkers such as brain natriuretic peptide. Further experience with these new markers pertaining to patient outcomes is necessary before firm recommendations can be proposed.
Supporting References: (32, 197, 198, 204-208)

Figure 2. Indications for AVR for Chronic AR

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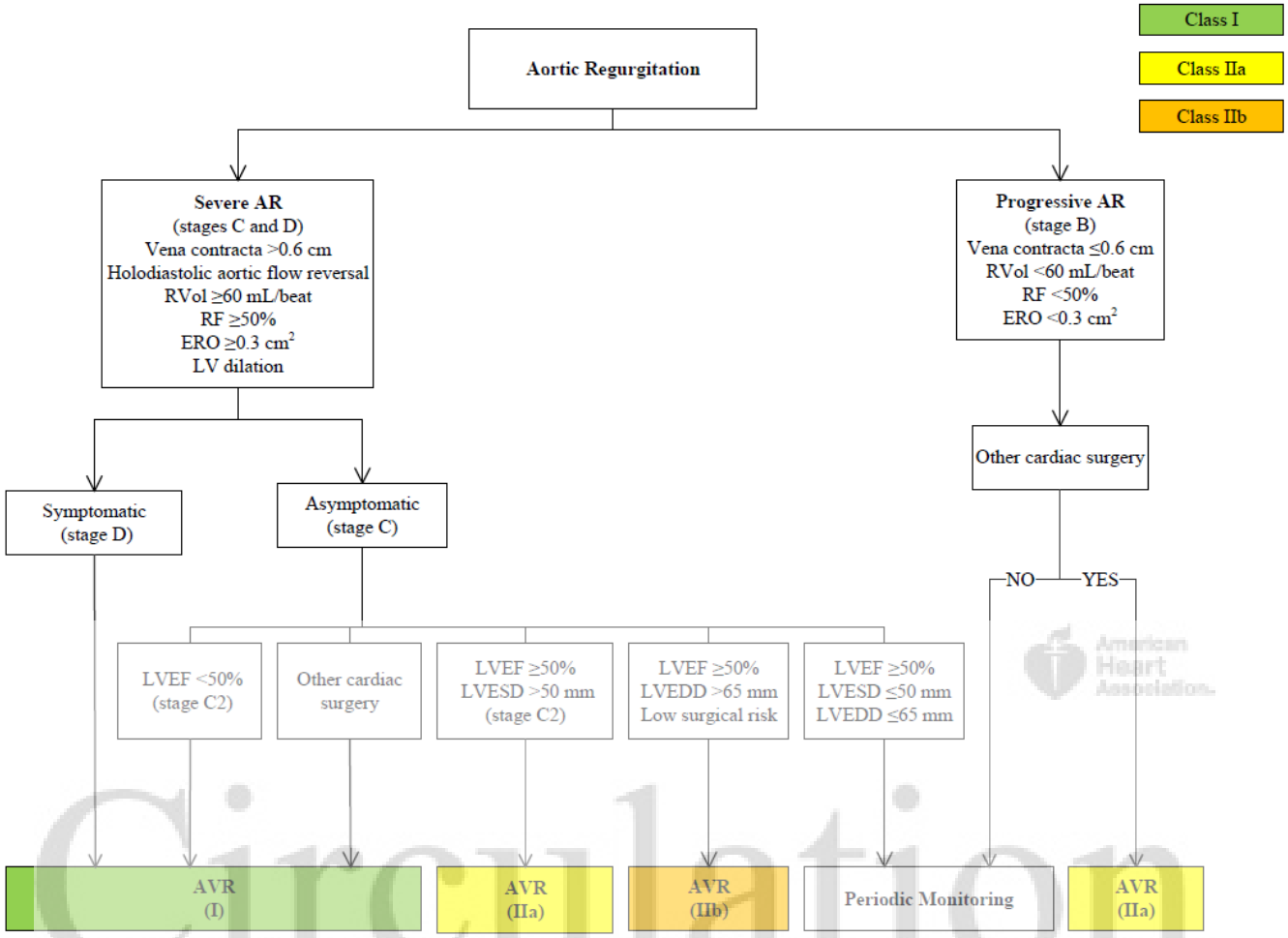

AR indicates aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; and RVol, regurgitant volume.

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5. Bicuspid Aortic Valve and Aortopathy

Patients with a bicuspid aortic valve may also have an associated aortopathy consisting of aortic dilation, coarctation, or even aortic dissection.

5.1. Bicuspid Aortic Valve

5.1.1. Diagnosis and Follow-Up

5.1.1.1. Diagnostic Testing—Initial Diagnosis: Recommendations

Class I

1. **An initial TTE is indicated in patients with a known bicuspid aortic valve to evaluate valve morphology, to measure the severity of AS and AR, and to assess the shape and diameter of the aortic sinuses and ascending aorta for prediction of clinical outcome and to determine timing of intervention (256-261). *(Level of Evidence: B)***

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Most patients with a bicuspid aortic valve will develop AS or AR over their lifetime. Standard echocardiographic approaches for measurement of stenosis and regurgitant severity are key to optimal patient management as detailed in the recommendations for AS and AR (Sections 3 and 4).

Bicuspid aortic valves are frequently associated with aortic dilation either at the level of the sinuses of Valsalva or, more frequently, in the ascending aorta. In some patients, severe aneurysmal aortic dilation may develop. The incidence of aortic dilation is higher in patients with fusion of the right and noncoronary cusps than the more common phenotype of fusion of the right and left coronary cusps. In a series of 191 patients with bicuspid aortic valves undergoing echocardiography, those with fusion of the right or left coronary cusp and the noncoronary cusp had a greater prevalence of aortic dilation than those with the fusion of the right and left coronary cusps (68% versus 40%). This was confirmed in a subsequent report of 167 patients with bicuspid aortic valves studied with CT and echocardiography. Patients with fusion involving the noncoronary cusp are also more likely to have dilation of the ascending aorta, rather than the sinuses, which often extends to the transverse arch.

In nearly all patients with a bicuspid aortic valve, TTE provides good quality images of the aortic sinuses with accurate diameter measurements. Further cephalad segments of the ascending aorta can be imaged in many patients by moving the transducer up 1 or 2 interspaces to view the arch from a suprasternal notch approach. The echocardiographic report should include aortic measurements at the aortic annulus, sinuses, sinotubular junction, and mid-ascending aorta, along with an indicator of the quality and completeness of aortic imaging in each patient with a bicuspid aortic valve. Doppler interrogation of the proximal descending aorta allows evaluation for aortic coarctation, which is associated with the presence of a bicuspid aortic valve.

In 20% to 30% of patients with bicuspid valves, other family members also have bicuspid valve disease and/or an associated aortopathy. A specific genetic cause has not been identified, and the patterns of inheritance are variable, so it is important to take a family history and inform patients that other family members may be affected. Imaging of first-degree relatives is clearly appropriate if the patient has an associated aortopathy or a family history of VHD or aortopathy. Many valve experts also recommend screening all first-degree relatives of patients with bicuspid aortic valve, although we do not yet have data addressing the possible impact of screening on outcomes or the cost-effectiveness of this approach.

Supporting References: (256-262)

Class I

2. **Aortic magnetic resonance angiography or CT angiography is indicated in patients with a bicuspid aortic valve when morphology of the aortic sinuses, sinotubular junction, or ascending aorta cannot be assessed accurately or fully by echocardiography. *(Level of Evidence: C)***

TTE can provide accurate assessment of the presence and severity of aortic dilation in most patients. However, in some patients, only the aortic sinuses can be visualized, because the ascending aorta is obscured by intervening lung tissue. When echocardiographic images do not provide adequate images of the ascending aorta to a distance ≥4.0 cm from the valve plane, additional imaging is needed. TEE may be considered but requires

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sedation and still may miss segments of the mid-ascending aorta. Magnetic resonance angiography or chest CT angiography provide accurate diameter measurements when aligned perpendicular to the long axis of the aorta. Advantages of magnetic resonance angiography and CT angiography compared with TTE include higher spatial (but lower temporal) resolution and the ability to display a 3D reconstruction of the entire length of the aorta. Magnetic resonance angiography and CT angiography aortic diameters typically are 1 mm to 2 mm larger than echocardiographic measurements because of inclusion of the aortic wall in the measurement and because echocardiographic measurements are made at end-diastole, whereas magnetic resonance angiography or CT angiography measurements may represent an average value. Magnetic resonance angiography imaging is preferred over CT angiography imaging, when possible, because of the absence of ionizing radiation exposure in patients who likely will have multiple imaging studies over their lifetime.

Supporting References: (262-264)

5.1.1.2. Diagnostic Testing—Routine Follow-Up: Recommendation

Class I

1. **Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or CT angiography is recommended in patients with a bicuspid aortic valve and an aortic diameter greater than 4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. In patients with an aortic diameter greater than 4.5 cm, this evaluation should be performed annually. *(Level of Evidence: C)***

Patients with bicuspid aortic valves who have documented dilation of the sinuses of Valsalva or ascending aorta should have serial assessment of aortic morphology because the aortopathy may progress with time. In a series of 68 patients with bicuspid aortic valves, the mean rate of diameter progression was 0.5 mm per year at the sinuses of Valsalva (95% CI: 0.3 to 0.7), 0.5 mm per year at the sinotubular junction (95% CI: 0.3 to 0.7), and 0.9 mm per year at the proximal ascending aorta (95% CI: 0.6 to 1.2). Others have reported mean rates of increase of up to 2 mm per year. Aortic imaging at least annually is prudent in patients with a bicuspid aortic valve and significant aortic dilation (>4.5 cm), a rapid rate of change in aortic diameter, and in those with a family history of aortic dissection. In patients with milder dilation that shows no change on sequential studies and a negative family history, a longer interval between imaging studies is appropriate.

Supporting References: (265-267)

5.1.2. Medical Therapy

There are no proven drug therapies that have shown to reduce the rate of progression of aortic dilation in patients with aortopathy associated with bicuspid aortic valve. In patients with hypertension, control of BP with any effective antihypertensive medication is warranted. Beta blockers and ARBs have conceptual advantages to reduce rate of progression but have not been shown to be beneficial in clinical studies.

5.1.3. Intervention: Recommendations

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Class I

1. **Operative intervention to repair the aortic sinuses or replace the ascending aorta is indicated in patients with a bicuspid aortic valve if the diameter of the aortic sinuses or ascending aorta is greater than 5.5 cm (113, 268, 269). *(Level of Evidence: B)***

In 2 large long-term retrospective cohort studies of patients with bicuspid aortic valves, the incidence of aortic dissection was very low. In a study of 642 patients followed for a mean of 9 years, there were 5 dissections (3 ascending and 2 descending). In another bicuspid aortic valve study of 416 patients followed for a mean of 16 years, there were 2 dissections. In the latter report, the calculated incidence of dissection was higher than the age-adjusted relative risk of the county's general population (HR: 8.4; 95% CI: 2.1 to 33.5; p=0.003) but was only 3.1 (95% CI: 0.5 to 9.5) cases per 10,000 patient-years. In patients with bicuspid aortic valves, data are limited regarding the degree of aortic dilation at which the risk of dissection is high enough to warrant operative intervention in patients who do not fulfill criteria for AVR on the basis of severe AS or AR. Previous ACC/AHA guidelines have recommended surgery when the degree of aortic dilation is >5.0 cm at any level, including sinuses of Valsalva, sinotubular junction, or ascending aorta. The current writing committee considers the evidence supporting these previous recommendations very limited and anecdotal and endorses a more individualized approach. Surgery is recommended with aortic dilation of 5.1 cm to 5.5 cm only if there is a family history of aortic dissection or rapid progression of dilation. In all other patients, operation is indicated if there is more severe dilation (5.5 cm). The writing committee also does not recommend the application of formulas to adjust the aortic diameter for body size. Furthermore, prior recommendations were frequently ambiguous with regard to the level to which they apply (sinus segment versus tubular ascending aorta) and did not acknowledge the normal difference in diameter at these levels, with the sinus segment 0.5 cm larger in diameter than the normal ascending aorta. In Heart Valve Centers of Excellence, valve-sparing replacement of the aortic sinuses and ascending aorta yields excellent results in patients who do not have severely deformed or dysfunctional valves.

Supporting References: (113, 245, 246, 267-274)

Class IIa

1. **Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with bicuspid aortic valves if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year). *(Level of Evidence: C)***

In patients with bicuspid aortic valves, data are limited regarding the degree of aortic dilation at which the risk of dissection is high enough to warrant operative intervention in patients who do not fulfill criteria for AVR on the basis of severe AS or AR. In patients at higher risk of dissection based on family history or evidence of rapid progression of aortic dilation (≥0.5 cm per year), surgical intervention is reasonable when the aortic diameter is >5.0 cm.

Supporting References: (267, 269-271, 275)

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Class IIa

2. **Replacement of the ascending aorta is reasonable in patients with a bicuspid aortic valve who are undergoing aortic valve surgery because of severe AS or AR (Sections 3.2.3 and 4.3.3) if the diameter of the ascending aorta is greater than 4.5 cm.** ***(Level of Evidence: C)***

In patients with bicuspid aortic valves, data are limited regarding the degree of aortic dilation at which the risk of dissection is high enough to warrant replacement of the ascending aorta at the time of AVR. The risk of progressive aortic dilation and dissection after AVR in patients with bicuspid aortic valves has been the subject of several studies, although definitive data are lacking. In patients undergoing AVR because of severe AS or AR, replacement of the ascending aorta is reasonable when the aortic diameter is >4.5 cm. Replacement of the sinuses of Valsalva is not necessary in all cases and should be individualized based on the displacement of the coronary ostia, because progressive dilation of the sinus segment after separate valve and graft repair is uncommon.

Supporting References: (267, 269-271, 276-280)

6. Mitral Stenosis

6.1. Stages of MS

Medical and interventional approaches to the management of patients with valvular MS depend on accurate diagnosis of the cause and stage of the disease process. Table 13 shows the stages of mitral valve disease ranging from patients at risk of MS (stage A) or with progressive hemodynamic obstruction (stage B) to severe asymptomatic (stage C) and symptomatic MS (stage D). Each of these stages is defined by valve anatomy, valve hemodynamics, the consequences of valve obstruction on the left atrium (LA) and pulmonary circulation, and patient symptoms. The anatomic features of the stages of MS are based on a rheumatic etiology for the disease. There are patients who have a nonrheumatic etiology of MS due to senile calcific disease (Section 6.3) in whom there is a heavily calcified mitral annulus with extension of the calcium into the leaflets. Hemodynamic severity is best characterized by the planimetered mitral valve area and the calculated mitral valve area from the diastolic pressure half-time. The definition of "severe" MS is based on the severity at which symptoms occur as well as the severity at which intervention will improve symptoms. Thus, a mitral valve area ≤ 1.5 cm^2 is considered severe. This usually corresponds to a transmitral mean gradient of >5 mm Hg to 10 mm Hg at a normal heart rate. However, the mean pressure gradient is highly dependent on the transvalvular flow and diastolic filling period and will vary greatly with changes in heart rate. The diastolic pressure half-time is dependent not only on the degree of mitral obstruction but also the compliance of the left ventricle and the LA and other measures of mitral valve area, such as the continuity equation or the proximal isovelocity surface area, may be used if discrepancies exist (281-287).

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Table 13. Stages of MS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	• Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA >1.5 cm^2	• Increased transmitral flow velocities • MVA >1.5 cm^2 • Diastolic pressure half-time <150 ms	• Mild-to-moderate LA enlargement • Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS)	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	None
D	Symptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• Decreased exercise tolerance • Exertional dyspnea

The transmitral mean pressure gradient should be obtained to further determine the hemodynamic effect of the MS and is usually >5 mm Hg to 10 mm Hg in severe MS; however, due to the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.

LA indicates left atrial; LV, left ventricular; MS, mitral stenosis; MVA, mitral valve area; and PASP, pulmonary artery systolic pressure.

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6.2. Rheumatic MS

See Figure 3 for indications for intervention for rheumatic MS.

6.2.1. Diagnosis and Follow-Up

6.2.1.1. Diagnostic Testing—Initial Diagnosis: Recommendations

Class I

1. **TTE is indicated in patients with signs or symptoms of MS to establish the diagnosis, quantify hemodynamic severity (mean pressure gradient, mitral valve area, and pulmonary artery pressure), assess concomitant valvular lesions, and demonstrate valve morphology (to determine suitability for mitral commissurotomy) (8, 143, 288-295). *(Level of Evidence: B)***

Suspicion for MS may arise from a childhood history of rheumatic fever or a characteristic auscultatory finding of an opening snap after the second heart sound and subsequent apical diastolic murmur, but such patients often present with nonspecific complaints of exertional dyspnea with an unrevealing physical examination. In the vast majority of cases, TTE can elucidate the anatomy and functional significance of MS but must be undertaken with great care. Use of 2D scanning from the parasternal long-axis window can identify the characteristic diastolic doming of the mitral valve, whereas short-axis scanning will demonstrate commissural fusion and allow planimetry of the mitral orifice. This must be done carefully to obtain the smallest orifice in space and the largest opening in time. Use of 3D echocardiography (either TTE or TEE) may allow greater accuracy but is not yet routinely used. Doppler hemodynamics are typically obtained from the apical 4-chamber or long-axis view and should include peak and mean transvalvular gradient as calculated by the simplified Bernoulli equation, averaged from 3 to 5 beats in sinus rhythm and 5 to 10 beats in AF. Heart rate should always be included in the report, because it greatly affects transvalvular gradient due to the differential impact of tachycardia on diastolic versus systolic duration. Concomitant MR should be sought and quantified as recommended, along with other valve lesions (Section 7.3.1.1). RV systolic pressure is typically estimated by continuous wave Doppler of TR. Mitral valve morphology and feasibility for percutaneous mitral balloon commissurotomy or surgical commissurotomy can be assessed in several ways, most commonly via the Wilkins score, which combines valve thickening, mobility, and calcification with subvalvular scarring in a 16-point scale. Characterization of commissural calcification is also useful. Additional echocardiographic tools for assessment of MS include the mitral pressure half-time, which is inversely related to mitral valve area. However, the mitral pressure half-time is also affected by left atrial and LV compliance. Thus, other methods for calculation of the mitral valve area, such as the continuity method and proximal isovelocity surface area method, could be used if necessary. Left atrial dimension, area, and volume index should be measured, with careful interrogation for possible left atrial thrombus (although full exclusion of thrombus requires TEE). As with any echocardiogram, full characterization of global and regional LV and RV function should be reported.

Supporting References: (8, 143, 288-295)

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Class I

2. **TEE should be performed in patients considered for percutaneous mitral balloon commissurotomy to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR (289, 296-298). *(Level of Evidence: B)***

TEE offers excellent visualization of the mitral valve and LA and is an alternative approach to assessment of MS in patients with technically limited transthoracic interrogation. Three-dimensional datasets may be acquired, from which optimal measurements of minimal orifice area can be obtained offline. However, in the vast majority of patients with MS, valve morphology and lesion severity can be obtained with TTE. A key exception is in patients being considered for percutaneous mitral balloon commissurotomy, in whom left atrial cavity and appendage thrombi must be excluded. Although TTE may identify risk factors for thrombus formation, several studies show that TTE has poor sensitivity for detecting such thrombi, thus mandating a TEE before percutaneous mitral balloon commissurotomy. Although TTE is generally accurate in grading MR, TEE may offer additional quantitation and assurance that MR >2+ is not present, which generally precludes percutaneous mitral balloon commissurotomy.

Supporting References: (289, 296-298)

6.2.1.2. Diagnostic Testing—Changing Signs or Symptoms

Patients with an established diagnosis of MS may experience a change in symptoms from progressive narrowing of the mitral valve, worsening of concomitant MR or other valve lesions, or a change in hemodynamic state due to such factors as AF, fever, anemia, hyperthyroidism, or postoperative state. In such cases, a TTE examination should be repeated to quantify the mitral valve gradient and area, as well as other parameters that may contribute to a change in symptoms.

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6.2.1.3. Diagnostic Testing—Routine Follow-Up

Rheumatic MS is a slowly progressive disease, characterized by a prolonged latent phase between the initial rheumatic illness and the development of valve stenosis. The latent phase is an interval typically measured in decades in the developed world but considerably shorter periods in the developing world, likely due to recurrent carditis. Once mild stenosis has developed, further narrowing is typical, although the rate of progression is highly variable. In 103 patients with MS followed for 3.3±2 years, valve area decreased at 0.09 cm^2 per year, although there was significant interpatient variability. Larger valves decreased in area more rapidly, although the same absolute decrease would be expected to have greater impact in the more stenotic valves. Importantly, progressive enlargement in the right ventricle and rise in RV systolic pressure were observed, even in the absence of a decrease in mitral valve area. Accordingly, repeat TTE at intervals dictated by valve area is an important aspect of disease management, even in patients without symptoms. TTE should be performed to re-evaluate asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure and valve gradient (very severe MS with mitral valve area <1.0 cm^2 every year, severe MS with mitral valve area ≤1.5 cm^2 every 1 to 2 years; and progressive MS with mitral valve area >1.5 cm^2 every 3 to 5 years) (Table 4).

Supporting References: (299-301)

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6.2.1.4. Diagnostic Testing—Cardiac Catheterization

In the contemporary era, adequate assessment of MS and associated lesions can be obtained in the vast majority of patients by TTE, occasionally supplemented by TEE. However, in those few patients with nondiagnostic studies or whose clinical and echocardiographic findings conflict, it is essential to further characterize MS hemodynamics and catheterization as the next best approach. Catheterization is also the only method available to measure absolute pressures inside the heart, which may be important in clinical decision making. Such studies must be carried out by personnel experienced with catheterization laboratory hemodynamics with simultaneous pressure measurements in the left ventricle and LA, ideally via transseptal catheterization. Although a properly performed mean pulmonary artery wedge pressure is an acceptable substitute for mean LA pressure, the LV to pulmonary wedge gradient will overestimate the true transmitral gradient due to phase delay and delayed transmission of pressure changes. The Gorlin equation is applied for calculation of mitral valve area, using cardiac output obtained via thermodilution (when there is no significant TR) or the Fick method. Ideally, measured oxygen consumption should be used in this calculation. Full right-heart pressures should be reported. In cases where exertional symptoms seem out of proportion to resting hemodynamic severity, data may be obtained during exercise.

Supporting References: (302-304)

6.2.1.5. Diagnostic Testing—Exercise Testing: Recommendation

Class I

1. **Exercise testing with Doppler or invasive hemodynamic assessment is recommended to evaluate the response of the mean mitral gradient and pulmonary artery pressure in patients with MS when there is a discrepancy between resting Doppler echocardiographic findings and clinical symptoms or signs. *(Level of Evidence: C)***

Exercise testing with hemodynamics yields a number of data points to help in the management of MS when a patient's symptoms seem significantly greater or less than would be expected from TTE. Results have been published using both exercise and dobutamine with Doppler echocardiography, although exercise is preferred in general as the more physiological test. Most experience is with treadmill exercise, with images and Doppler obtained immediately after stress, but bicycle exercise allows data acquisition at various stages of exercise. Bicycle or arm ergometry exercise testing during cardiac catheterization can also be performed for direct measurements of pulmonary artery wedge pressure and pulmonary pressures at rest and with exercise. Simple functional capacity is important to help quantify the patient's symptoms and assess changes over time. Changes in valve gradient are also helpful, as is the presence of exercise-induced pulmonary hypertension. Although exercise-induced pulmonary hypertension does not have a formal place in these guidelines, a rise in RV systolic pressure to >60 mm Hg to 70 mm Hg should prompt the clinician to carefully consider the patient's symptoms. Most patients can continue to be followed without exercise testing by careful clinical assessment and periodic resting echocardiograms as indicated above.

Supporting References: (305-308)

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6.2.2. Medical Therapy: Recommendations

Class I

1. **Anticoagulation (vitamin K antagonist [VKA] or heparin) is indicated in patients with 1) MS and AF (paroxysmal, persistent, or permanent), or 2) MS and a prior embolic event, or 3) MS and a left atrial thrombus (309-315).** ***(Level of Evidence: B)***

In the presurgical era, patients with MS were at high risk for arterial embolization, which was further elevated in those with AF and prior embolic events. Anticoagulation with VKA has long been recommended for patients with MS with AF or prior embolism and has been so well accepted that patients with MS have generally been excluded from AF trials examining the utility of anticoagulation. One exception to trials excluding patients with MS is the NASPEAF (National Study for Prevention of Embolism in Atrial Fibrillation) trial. Of the 495 high-risk patients in the cohort, 316 patients had MS. Of these 316 patients, 95 had a prior embolization. Patients in the study were randomized to standard anticoagulation with VKA (international normalized ratio [INR] goal 2 to 3) versus the combination of an antiplatelet agent and VKA anticoagulation with a lower INR goal (0.10 to 2.5). The study demonstrated a highly significant increased risk for embolism among those patients with VHD with prior events versus those without (9.1% versus 2.3% over 3 years; $p<0.001$). Further larger studies are required to determine if antiplatelet agents should be used in patients with AF and MS. Although no trial evidence exists for anticoagulation when LA or left atrial appendage thrombi are incidentally found (generally by TEE), it is well documented that even in sinus rhythm, such clots are predisposed to embolize, and so anticoagulation with VKA is recommended. Anticoagulation should be given indefinitely to patients with these indications. It is controversial as to whether long-term anticoagulation should be given to patients with MS in normal sinus rhythm on the basis of left atrial enlargement or spontaneous contrast on TEE. The efficacy of the novel oral anticoagulant agents in preventing embolic events has not been studied in patients with MS.

Supporting References: (309-315)

Class IIa

1. **Heart rate control can be beneficial in patients with MS and AF and fast ventricular response.** ***(Level of Evidence: C)***

Patients with MS are prone to developing atrial arrhythmias. Thirty percent to 40% of patients with severe MS will develop AF. Significant detrimental hemodynamic consequences may be associated with the acute development of AF, primarily from the rapid ventricular response, which shortens the diastolic filling period and increases left atrial pressure. The treatment of acute AF is anticoagulation and control of the heart rate response with negative dromotropic agents. If the rate cannot be adequately controlled with medications, cardioversion may be necessary to improve hemodynamics. In the stable patient, the decision for rate control versus rhythm control is dependent on multiple factors, including the duration of AF, hemodynamic response to AF, left atrial size, prior episodes of AF, and a history of embolic events. It is more difficult to achieve rhythm control in

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patients with MS because the rheumatic process itself may lead to fibrosis of the intermodal and interatrial tracts and damage to the sinoatrial node.

Supporting References: (316)

Class IIb

1. **Heart rate control may be considered for patients with MS in normal sinus rhythm and symptoms associated with exercise (317, 318). *(Level of Evidence: B)***

It is well known that the proportion of the cardiac cycle occupied by diastole decreases with increasing heart rate, thereby increasing the mean flow rate across the mitral valve (assuming constant cardiac output) with a consequent rise in mean mitral gradient in MS in proportion to the square of the flow rate. A study of normal volunteers undergoing bicycle exercise echocardiography demonstrated a reduction in the diastolic interval from 604 milliseconds to 219 milliseconds as the heart rate increased from 60 bpm to 120 bpm, indicating a 63% reduction in total diastolic time. Maintaining the same cardiac output would require a 38% increase in mean flow rate during diastole, which, by squared relation of the Bernoulli equation, requires an increase in mean mitral gradient of approximately 90%. Thus, it is rational to think that limiting tachycardia with beta blockade might be beneficial in patients with MS in normal sinus rhythm. Nevertheless, the only RCT on the impact of beta blockade on exercise duration in MS failed to show this salutary effect. One study looked at 15 patients with an average mitral area of 1.0 cm^2 (NYHA class II and III) randomized in crossover fashion to atenolol or placebo. Although the exercise heart rate was significantly reduced and diastolic filling interval increased by 40%, there was no increase in functional capacity, and maximal O_2 consumption actually fell by 11%, with cardiac index falling by 20% when patients were treated with beta blockade. One study had more neutral results in a trial of 17 patients with NYHA class I and II MS, and 7 patients had improvement in maximal oxygen consumption, whereas 4 had a deterioration in symptoms. Overall, anaerobic threshold was reduced by 11% with atenolol therapy, so these studies do not support the general use of heart rate control in patients with MS and normal sinus rhythm. Nevertheless, in selected patients whose symptoms worsen markedly with exercise, a trial of beta blockade might be considered. Other negative chronotropic agents have not been evaluated in patients with MS.

Supporting Reference: (317, 318)

6.2.3. Intervention: Recommendations

See Table 14 for a summary of recommendations from this section.

Table 14. Summary of Recommendations for MS Intervention

Recommendations	COR	LOE	References
PMBC is recommended for symptomatic patients with severe MS (MVA $\leq$1.5 cm^2, stage D) and favorable valve morphology in the absence of contraindications	I	A	(281-285, 287)
Mitral valve surgery is indicated in severely symptomatic patients (NYHA class III/IV) with severe MS (MVA $\leq$1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC	I	B	(319-324)

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Concomitant mitral valve surgery is indicated for patients with severe MS (MVA ≤1.5 cm^2, stage C or D) undergoing other cardiac surgery	I	C	N/A
PMBC is reasonable for asymptomatic patients with very severe MS (MVA ≤1.0 cm^2, stage C) and favorable valve morphology in the absence of contraindications	IIa	C	(293, 325-327)
Mitral valve surgery is reasonable for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D), provided there are other operative indications	IIa	C	N/A
PMBC may be considered for asymptomatic patients with severe MS (MVA ≤1.5 cm^2, stage C) and favorable valve morphology who have new onset of AF in the absence of contraindications	IIb	C	N/A
PMBC may be considered for symptomatic patients with MVA >1.5 cm^2 if there is evidence of hemodynamically significant MS during exercise	IIb	C	N/A
PMBC may be considered for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who have suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery	IIb	C	N/A
Concomitant mitral valve surgery may be considered for patients with moderate MS (MVA 1.6–2.0 cm^2) undergoing other cardiac surgery	IIb	C	N/A
Mitral valve surgery and excision of the left atrial appendage may be considered for patients with severe MS (MVA ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation	IIb	C	N/A

AF indicates atrial fibrillation; COR, Class of Recommendations; LOE, Level of Evidence; MS, mitral stenosis; MVA, mitral valve area; NYHA, New York Heart Association; and PMBC, percutaneous mitral balloon commissurotomy.

Class I

1. **Percutaneous mitral balloon commissurotomy is recommended for symptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (281-285, 287, 328). *(Level of Evidence: A)***

Several RCTs have established the safety and efficacy of percutaneous balloon mitral commissurotomy compared with surgical closed or open commissurotomy. The technique is generally performed by advancing 1 or more balloon catheters across the mitral valve and inflating them, thereby splitting the commissures. For the percutaneous approach to have optimal outcome, it is essential that the valve morphology be predictive of success, generally being mobile, relatively thin, and free of calcium. This is usually assessed by the Wilkins score, although other risk scores have also shown utility. Clinical factors such as age, NYHA class, and presence or absence of AF are also predictive of outcome. Percutaneous mitral balloon commissurotomy should be performed by experienced operators with immediate availability of surgical backup for potential complications. Percutaneous mitral balloon commissurotomy is also useful in patients with restenosis following prior commissurotomy if restenosis is the consequence of refusion of both commissures.

Supporting References: (281-285, 287, 292, 294, 325, 328-331)

See Online Data Supplement 13 for a summary of RCTs that have established the safety and efficacy of percutaneous mitral balloon commissurotomy in comparison to surgical closed or open commissurotomy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

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2. **Mitral valve surgery (repair, commissurotomy, or valve replacement) is indicated in severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area ≤1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or who have failed previous percutaneous mitral balloon commissurotomy (319-324).** ***(Level of Evidence: B)***

Mitral valve surgery is an established therapy for MS, predating percutaneous mitral balloon commissurotomy. Surgical options may involve commissurotomy (either closed, where the valve is opened blindly through the LA or left ventricle, or open, which allows more extensive surgery under direct visualization). MVR may be preferred in the presence of severe valvular thickening and subvalvular fibrosis with leaflet tethering. In addition to those who have suboptimal valve anatomy (or failed percutaneous mitral balloon commissurotomy), patients with moderate or severe TR may also have a better outcome with a surgical approach that includes tricuspid valve repair. Because the natural history of MS is one of slow progression over decades and MS does not have long-standing detrimental effects on the left ventricle, surgery should be delayed until the patient has severe limiting symptoms (NYHA class III to IV).

Supporting References: (284, 319-324, 332-334)

Class I

3. **Concomitant mitral valve surgery is indicated for patients with severe MS (mitral valve area ≤1.5 cm^2, stage C or D) undergoing cardiac surgery for other indications.** ***(Level of Evidence: C)***

Studies of the natural history of moderate-to-severe MS demonstrate progressive decrement in valve area of 0.09 cm^2 per year. For patients with other indications for open heart surgery, mitral intervention should be undertaken, particularly in those patients with valves amenable to open commissurotomy or valve repair.

Supporting Reference: (300)

Class IIa

1. **Percutaneous mitral balloon commissurotomy is reasonable for asymptomatic patients with very severe MS (mitral valve area ≤1.0 cm^2, stage C) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (293, 325-327).** ***(Level of Evidence: C)***

Although it is a general rule in VHD not to intervene before the onset of symptoms, there are patients who will clearly benefit from intervention while still ostensibly asymptomatic. Most patients with mitral valve area ≤1.0 cm^2 will manifest a true reduction in functional capacity even if the gradual onset is not obvious. In addition, numerous studies have demonstrated a greater likelihood of successful percutaneous mitral balloon commissurotomy when the valve is less thickened and calcified, indicating intervention before this state. Furthermore, it is preferable to intervene before the development of severe pulmonary hypertension, because those patients with near systemic pulmonary pressure show reduced RV function and persistent pulmonary hypertension following percutaneous mitral balloon commissurotomy or MVR.

Supporting References: (293, 325-327)

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Class IIa

2. **Mitral valve surgery is reasonable for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area ≤1.5 cm^2, stage D), provided there are other operative indications (e.g., aortic valve disease, CAD, TR, aortic aneurysm).** ***(Level of Evidence: C)***

A situation may arise in which a patient who is otherwise a candidate for percutaneous mitral balloon commissurotomy (favorable valve anatomy, no atrial thrombus or significant MR) has other cardiac conditions that should be addressed surgically. These patients should undergo a comprehensive operation to address all lesions, including MS. However, as percutaneous intervention has evolved, particularly that involving the coronary arteries and aortic valve, there will be circumstances in which an all-percutaneous approach will be favored. This decision should take into account the local expertise at the treating facility.

Class IIb

1. **Percutaneous mitral balloon commissurotomy may be considered for asymptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage C) and valve morphology favorable for percutaneous mitral balloon commissurotomy in the absence of left atrial thrombus or moderate-to-severe MR who have new onset of AF.** ***(Level of Evidence: C)***

Patients with mild and asymptomatic MS may develop AF as an isolated event that can be managed without mitral valve intervention for many years. However, in many patients, the onset of AF may be a harbinger of a more symptomatic phase of the disease. Percutaneous mitral balloon commissurotomy may be considered in such cases, particularly if rate control is difficult to achieve or if the mitral valve area is ≤1.5 cm^2. Lowering the left atrial pressure by percutaneous mitral balloon commissurotomy may be useful if a rhythm control approach is taken for AF.

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Class IIb

2. **Percutaneous mitral balloon commissurotomy may be considered for symptomatic patients with mitral valve area greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery wedge pressure greater than 25 mm Hg or mean mitral valve gradient greater than 15 mm Hg during exercise.** ***(Level of Evidence: C)***

It is recognized that there are patients with genuine symptoms from MS, even with mitral valve area between 1.6 cm^2 and 2.0 cm^2, who would benefit from percutaneous mitral balloon commissurotomy. This may occur for several reasons. First, given the vagaries of clinical imaging, it is possible that the valve is actually smaller than the reported area. Second, for a given valve area, the transmitral gradient will be higher in persons with a large body surface area or those with other reasons to have an elevated cardiac output (e.g., arteriovenous fistulae). Third, there is a variable relation of pulmonary vascular resistance in comparison to mitral valve area. Thus, patients may experience clinical improvement in such cases. This procedure may be performed for these indications in patients with valve morphology suitable for percutaneous mitral balloon commissurotomy.
Supporting Reference: (335)

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Class IIb

3. **Percutaneous mitral balloon commissurotomy may be considered for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area ≤1.5 cm^2, stage D) who have a suboptimal valve anatomy and who are not candidates for surgery or at high risk for surgery. *(Level of Evidence: C)***

Both the Wilkins score and the presence of commissural calcification predict successful percutaneous mitral balloon commissurotomy. However in all such series, this predictive ability is not absolute, with 42% of patients with a Wilkins score >8 having an optimal outcome (25% increase in mitral valve area to >1.5 cm^2) and 38% of patients with commissural calcium having event-free survival at 1.8 years. Accordingly, severely symptomatic patients who are poor surgical candidates may benefit from percutaneous mitral balloon commissurotomy even with suboptimal valve anatomy. Patients who refuse surgery may also be considered for percutaneous mitral balloon commissurotomy after discussion about the potential complications associated with this procedure when performed in patients with suboptimal valve anatomy.

Supporting References: (292-294)

Class IIb

4. **Concomitant mitral valve surgery may be considered for patients with moderate MS (mitral valve area 1.6 cm^2 to 2.0 cm^2) undergoing cardiac surgery for other indications. *(Level of Evidence: C)***

Consideration of concomitant MVR at the time of other heart surgery must balance several factors, including the severity of MS (based on mitral valve area, mean pressure gradient, and pulmonary arterial pressure); rate of progression; history of AF; skill of the surgeon; and perceived risk of repeat cardiac surgery if the MS progresses to a symptomatic state. Consideration should also include the suitability of the valve for subsequent percutaneous mitral balloon commissurotomy (echocardiogram score and presence of MR), as this might be a preferable method for treating worsening MS.

Class IIb

5. **Mitral valve surgery and excision of the left atrial appendage may be considered for patients with severe MS (mitral valve area ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation. *(Level of Evidence: C)***

A large prospective study of patients with MS shows an elevated risk of recurrent embolism among patients with prior embolic events irrespective of the presence or absence of AF. The risk is reduced, but not eliminated, by percutaneous mitral balloon commissurotomy. Another study of 205 patients who underwent mitral valve surgery, 58 with ligation of the left atrial appendage, demonstrated that lack of ligation was significantly associated with future embolic events (odds ratio [OR]: 6.7). This study also noted that in 6 of the 58 ligation patients, communication of the left atrial appendage and LA cavity was still present. Residual communication between the left atrial appendage and LA cavity was noted in 60% of patients undergoing left atrial appendage ligation in a subsequent study, suggesting that left atrial appendage excision and not ligation may be the preferred approach in selected patients.

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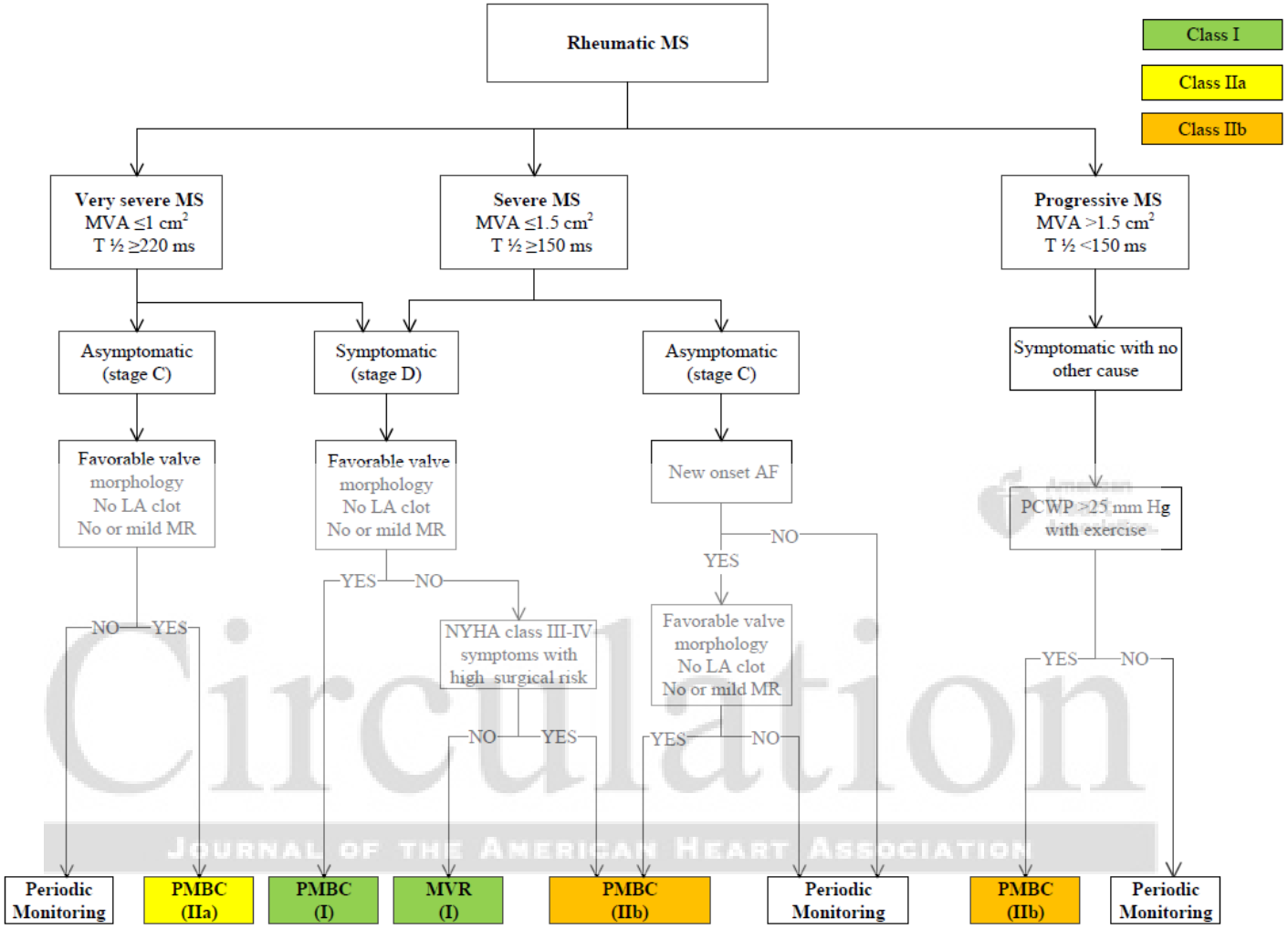
Supporting References: (336, 337)

Figure 3. Indications for Intervention for Rheumatic MS



AF indicates atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time.

See Online Data Supplements 14 and 15 for more information on the outcomes of percutaneous mitral balloon commissurotomy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

6.3. Nonrheumatic MS

Although the vast majority of MS in the world results from rheumatic heart disease, senile calcific MS is found with increasing frequency in the elderly population in North America. This is due to calcification of the mitral annulus and calcification that extends into the leaflets, which cause both a narrowing of the annulus and rigidity of the leaflets without commissural fusion. Mitral annular calcification has been associated with decreased renal function and inflammatory markers like C-reactive protein; however, senile calcific MS is common in the elderly population with normal renal function and is associated with senile AS. Data are relatively sparse on the natural history of senile calcific MS. A small study of 32 patients observed over a mean of 2.6 years

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demonstrated progression in mean mitral valve gradient in only half of the subjects. However, in those with progression, the rate of change averaged 2 mm Hg per year and changed as rapidly as 9 mm Hg per year. More rapid progression was found in younger patients, but surprisingly this was not predicted by a reduced glomerular filtration rate. Although the mean pressure gradient from Doppler echocardiography is accurate, the use of a mitral valve area from diastolic half-time is uncertain in this population. Indications for intervention in patients with senile calcific MS are different from those for rheumatic MS for the following reasons. First, because calcification involves the annulus and base of the leaflets without commissural fusion, there is no role for percutaneous mitral balloon or surgical commissurotomy. Second, the presence of severe mitral annular calcification can be quite challenging for the surgeon because it causes problems in securely attaching the prosthetic valve and narrowing of the orifice. Supra-annular insertion and other innovative techniques can be used, such as placement of a felt patch around the valve orifice to anchor the prosthesis; however, this only works if the mitral orifice is adequate. If the annular calcification narrows the orifice, it has to be debrided. The other alternative is left atrial to ventricular bypass with a valved conduit in extreme cases of calcification both of the leaflet and the annulus. Finally, patients with calcification are often elderly and debilitated, have multiple comorbidities, and are at high risk for surgery. For these reasons, intervention should be delayed until symptoms are severely limiting and cannot be managed with diuresis and heart rate control.

A subset of patients have mitral inflow obstruction due to other causes, such as congenital malformations, tumors, or other masses. Congenital MS usually takes the form of a parachute mitral valve, where the mitral chordae are attached to a single or dominant papillary muscle and often form a component of the Shone complex, which can include supramitral rings, valvular or subvalvular AS, and aortic coarctation. For MS caused by tumors or other obstructive lesions, intervention is aimed at reducing or removing the mass, with efforts made to preserve the valve.

Supporting References: (338-352)

7. Mitral Regurgitation

7.1. Acute MR

Acute MR may be due to disruption of different parts of the mitral valve apparatus. IE may cause leaflet perforation or chordal rupture. Spontaneous chordal rupture may occur in patients with degenerative mitral valve disease. Rupture of the papillary muscle occurs in patients who have an acute ST-segment elevation MI usually associated with an inferior infarction. The acute volume overload on the left ventricle and LA results in pulmonary congestion and low forward cardiac output. Diagnosis of the presence and etiology of acute MR and urgent intervention may be lifesaving.

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7.1.1. Diagnosis and Follow-Up

TTE is useful in patients with severe acute *primary* MR for evaluation of LV function, RV function, pulmonary artery pressure, and mechanism of MR. The patient with severe acute MR, which might occur from chordal rupture, usually experiences acute decompensation with hemodynamic embarrassment. The sudden volume overload increases left atrial and pulmonary venous pressure, leading to pulmonary congestion and hypoxia, whereas decreased blood delivery to the aorta causes reduced cardiac output, hypotension, or even shock. The rapid systolic rise in LA pressure with a concomitant fall in LV systolic pressure limits the pressure gradient driving MR to early systole. Thus, the murmur may be short and unimpressive. Some patients with severe torrential MR have no murmur due to equalization of the LV and left atrial pressures. TTE can usually clarify the diagnosis by demonstrating the presence of severe MR, the mechanism causing MR, and a hyperdynamic instead of a depressed left ventricle as would be present in many other causes of hemodynamic compromise. Likely mechanisms of acute MR detected by TTE include valve disruption or perforation from IE, chordal rupture, and/or papillary muscle rupture. If the diagnosis of IE as the cause of acute MR is made, therapy that includes antibiotic administration and early surgery must be considered.

It may be difficult to diagnose severe acute MR with TTE due to narrow eccentric jets of MR, tachycardia, and early equalization of LV and LA pressures. In cases where TTE is nondiagnostic but the suspicion of severe acute MR persists, enhanced mitral valve imaging with TEE usually clarifies the diagnosis. TEE can be especially helpful in detecting valvular vegetations and annular abscesses that may further accentuate the need for a more urgent surgical approach. In the presence of sudden acute and hemodynamic instability after MI with hyperdynamic LV function by TTE and no other cause for the deterioration, TEE should be performed as soon as possible, looking for severe MR due either to a papillary muscle or chordal rupture.

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7.1.2. Medical Therapy

Vasodilator therapy can be useful to improve hemodynamic compensation in acute MR. The premise of use of vasodilators in acute MR is reduction of impedance of aortic flow, thereby preferentially guiding flow away from the left ventricle to the left atrial regurgitant pathway, decreasing MR while simultaneously increasing forward output. This is usually accomplished by infusion of an easily titratable agent such as sodium nitroprusside or nicardipine. Use of vasodilators is often limited by systemic hypotension that is exacerbated when peripheral resistance is decreased.

Intra-aortic balloon counterpulsation can be helpful to treat acute severe MR. By lowering systolic aortic pressure, intra-aortic balloon counterpulsation decreases LV afterload, increasing forward output while decreasing regurgitant volume. Simultaneously, intra-aortic balloon counterpulsation increases diastolic and mean aortic pressure, thereby supporting the systemic circulation. In almost every case, intra-aortic balloon counterpulsation is a temporizing measure for achieving hemodynamic stability until definitive mitral surgery

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can be performed. The use of a percutaneous circulatory assist device may also be effective to stabilize a patient with acute hemodynamic compromise before operation.

Supporting References: (353, 354)

7.1.3. Intervention

Prompt mitral valve surgery is recommended for treatment of the symptomatic patient with acute severe *primary* MR. The severity of acute *primary* MR is variable, and some patients with more moderate amounts of MR may develop compensation as LV dilation allows for lower filling pressure and increased forward cardiac output. However, most patients with acute severe MR will require surgical correction for re-establishment of normal hemodynamics and for relief of symptoms. This is especially true for a complete papillary muscle rupture that causes torrential MR, which is poorly tolerated. Even if there is a partial papillary muscle rupture with hemodynamic stability, urgent surgery is indicated because these can suddenly progress to complete papillary muscle rupture. In cases of ruptured chordae tendineae, mitral repair is usually feasible and preferred over MVR, and the timing of surgery can be determined by the patient's hemodynamic status. If IE is the cause of severe symptomatic MR, earlier surgery is generally preferred because of better outcomes over medical therapy. However, this strategy should also be tempered by the patient's overall condition.

Supporting Reference: (355)

7.2. Stages of Chronic MR

In assessing the patient with chronic MR, it is critical to distinguish between chronic *primary* (degenerative) MR and chronic *secondary* (functional) MR, as these 2 conditions have more differences than similarities.

In chronic *primary* MR, the pathology of ≥1 of the components of the valve (leaflets, chordae tendineae, papillary muscles, annulus) causes valve incompetence with systolic regurgitation of blood from the left ventricle to the LA (Table 15). The most common cause of chronic *primary* MR in developed countries is mitral valve prolapse, which has a wide spectrum of etiology and presentation. Younger populations present with severe myxomatous degeneration with gross redundancy of both anterior and posterior leaflets and the chordal apparatus (Barlow's valve). Alternatively, older populations present with fibroelastic deficiency disease, in which lack of connective tissue leads to chordal rupture. The differentiation between these 2 etiologies has important implications for operative intervention. Other less common causes of chronic *primary* MR include IE, connective tissue disorders, rheumatic heart disease, cleft mitral valve, and radiation heart disease. If the subsequent volume overload of chronic *primary* MR is prolonged and severe, it causes myocardial damage, HF, and eventual death. Correction of the MR is curative. Thus, MR is "the disease."

In chronic *secondary* MR, the mitral valve is usually normal (Table 16). Instead, severe LV dysfunction is caused either by CAD, related MI (ischemic chronic *secondary* MR), or idiopathic myocardial disease (nonischemic chronic *secondary* MR). The abnormal and dilated left ventricle causes papillary muscle displacement, which in turn results in leaflet tethering with associated annular dilation that prevents coaptation. Because MR is only 1 component of the disease (severe LV dysfunction, coronary disease, or idiopathic

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myocardial disease are the others), restoration of mitral valve competence is not by itself curative; thus, the best therapy for chronic *secondary* MR is much less clear than it is for chronic *primary* MR. The data are limited, and there is greater difficulty in defining the severity of MR in patients with *secondary* MR than in those with *primary* MR. In patients with *secondary* MR, adverse outcomes are associated with a smaller calculated effective regurgitant orifice compared to *primary* MR due to multiple reasons. The MR will likely progress because of the associated progressive LV systolic dysfunction and adverse remodeling. In addition, there is an underestimation of effective regurgitant orifice area by the 2D echocardiography–derived flow convergence method due to the crescentic shape of the regurgitant orifice. There are the additional clinical effects of a smaller amount of regurgitation in the presence of compromised LV systolic function and baseline elevated filling pressures.

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Table 15. Stages of *Primary* MR

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	At risk of MR	• Mild mitral valve prolapse with normal coaptation • Mild valve thickening and leaflet restriction	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.3 cm	• None	• None
B	Progressive MR	• Severe mitral valve prolapse with normal coaptation • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE	• Central jet MR 20%–40% LA or late systolic eccentric jet MR • Vena contracta <0.7 cm • Regurgitant volume <60 mL • Regurgitant fraction <50% • ERO <0.40 cm^2 • Angiographic grade 1–2+	• Mild LA enlargement • No LV enlargement • Normal pulmonary pressure	• None
C	Asymptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension may be present at rest or with exercise • **C1:** LVEF >60% and LVESD <40 mm • **C2:** LVEF ≤60% and LVESD ≥40 mm	• None
D	Symptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension present	• Decreased exercise tolerance • Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

ERO indicates effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD; left ventricular end-systolic dimension; and MR, mitral regurgitation.

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Table 16. Stages of *Secondary* MR

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.30 cm	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• ERO <0.20 cm^2† • Regurgitant volume <30 mL • Regurgitant fraction <50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥0.20 cm^2 † • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥0.20 cm^2† • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• HF symptoms due to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.
†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

2D indicates 2-dimensional; ERO, effective regurgitant orifice; HF, heart failure; LA, left atrium; LV, left ventricular; MR, mitral regurgitation; and TTE, transthoracic echocardiogram.

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7.3. Chronic Primary MR

7.3.1. Diagnosis and Follow-Up

7.3.1.1. Diagnostic Testing—Initial Diagnosis: Recommendations

Class I

1. **TTE is indicated for baseline evaluation of LV size and function, RV function and left atrial size, pulmonary artery pressure, and mechanism and severity of primary MR (stages A to D) in any patient suspected of having chronic primary MR (5, 21, 39, 356-371). *(Level of Evidence: B)***

Images provided by TTE generate most of the diagnostic data needed for clinical decision making in chronic primary MR. The outcome of the patient with chronic primary MR is determined by lesion severity and the presence or absence of negative prognostic features that include the presence of symptoms, onset of LV dysfunction, and presence of pulmonary hypertension; usually only severe MR leads to these negative sequelae. Favorable loading conditions in MR (increased preload and usually normal afterload) increase ejection phase indexes of LV function, such as LVEF, but do not affect the extent of shortening. Thus, a "normal" LVEF in MR is approximately 70%. In turn, the onset of LV dysfunction is inferred when LVEF declines toward 60% or when the left ventricle is unable to contract to <40 mm diameter at end systole. It is clear that properly obtained and validated chamber volumes give more information about detrimental cardiac remodeling than simple chamber dimensions, as suggested by angiographically obtained volume data. These techniques have been replaced by newer noninvasive imaging techniques, which initially used chamber dimensions for measurement of LV size and function. Until more prognostic volumetric data are available, most current prognostic data rely on chamber dimensions. Pulmonary artery systolic pressure approaching 50 mm Hg also worsens prognosis. Thus, when the murmur of MR is first discovered, the clinician needs to know the severity of the MR (Table 15) and the size and function of the left ventricle, pulmonary artery pressure, and valve pathoanatomy from which valve reparability can be predicted. Determination of the severity of MR should be made on the basis of measurements of effective orifice area, regurgitant volume, and regurgitant fraction using the proximal isovelocity surface area or quantitative Doppler flow measurements. However, there are limitations to this technique, and multiple Doppler parameters, including color jet area, vena contracta, continuous wave Doppler intensity, and transmitral jet velocity curve should be used to correlate with the quantitative measurements. Once one of the above "triggers" is reached, indicating severe MR and LV dysfunction, the patient should be considered for mitral valve surgery. TTE serves to give this information in most cases and also generates baseline data that can be used to compare the patient's progress on subsequent examinations. Three-dimensional echocardiography, strain imaging, or CMR may add more accurate assessment of the LV response in the future. Symptom presence is a key determinant of outcome, yet symptom status is highly subjective. Studies have demonstrated a correlation between B-type natriuretic peptide and outcome in MR. Although the data are

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preliminary, the finding of a rising B-type natriuretic peptide could be helpful as another factor in deciding the optimal timing of mitral surgery.

Supporting References: (5, 21, 39, 356-371)

Class I

2. **CMR is indicated in patients with chronic primary MR to assess LV and RV volumes, function, or MR severity and when these issues are not satisfactorily addressed by TTE (366, 372, 373). (*Level of Evidence: B)***

In most cases, TTE provides the data needed for adequate evaluation of the MR patient. However, in cases where TTE image quality is poor, CMR may be of value in MR evaluation. CMR produces highly accurate data on LV volumes, RV volumes, and LVEF, and an estimation of MR severity, but outcome data using CMR volumes is pending. CMR is less helpful in establishing mitral pathoanatomy.

Supporting References: (366, 372, 373)

Class I

3. **Intraoperative TEE is indicated to establish the anatomic basis for chronic primary MR (stages C and D) and to guide repair (374, 375). *(Level of Evidence: B)***

Intraoperative TEE is a standard imaging modality for the surgical therapy of MR. Before the operative incision, TEE may give the surgeon a better understanding of the valve anatomy and type of repair that will likely be performed, although this decision is ultimately made when the valve is inspected visually. Three-dimensional TEE may be helpful in further visualizing the abnormal mitral valve anatomy. Because anesthesia lessens afterload, preload, and mitral valve closing force, it is important that decisions about severity of MR not be reevaluated under these artificial conditions, in which MR severity could be underestimated.

Intraoperative TEE is especially helpful in gauging the adequacy of repair. Because even mild residual MR after repair worsens the likelihood of later repair failure necessitating reoperation, surgeons strive for near-perfect operative repair. If MR is detected in the operating room following repair, it is often an indication that the repair should be revised. This assessment should be made during conditions that approach those of normal physiology. The left ventricle should be well filled and systemic BP should be brought well into the normal range. A low preload with underfilling of the left ventricle can lead to 1) systolic anterior leaflet motion with outflow obstruction or 2) underestimation of degree of residual MR. Thus, information obtained by TEE when the ventricle is underfilled can lead to an unneeded revision in the former case while overlooking a needed revision in the latter. Intraoperative TEE is also useful for diagnosing mitral inflow obstruction or LV outflow obstruction as a result of the mitral valve repair.

Supporting References: (374, 375)

Class I

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4. **TEE is indicated for evaluation of patients with chronic primary MR (stages B to D) in whom noninvasive imaging provides nondiagnostic information about severity of MR, mechanism of MR, and/or status of LV function.** ***(Level of Evidence: C)***

TEE is not recommended for routine evaluation and follow-up of patients with chronic primary MR but is indicated in specific situations. Because TEE provides excellent imaging of the mitral valve, it should be performed when TTE images are inadequate. TEE is especially useful in cases of MR due to IE, where additional information about other potentially infected structures can be fully evaluated by that technique. TEE allows more precise quantitation of regurgitant severity and provides a better estimate of the likelihood of a successful surgical valve repair. Three-dimensional TEE may be helpful in further visualizing the abnormal mitral valve anatomy. Mitral valve repair is preferable to valve replacement because of lower operative mortality and avoidance of the complications inherent to prosthetic valves that accrue over time. Thus, if repair can be accomplished, it might be performed earlier in the course of disease. Alternatively, if replacement is likely, strategy shifts toward performing surgery later to avoid unwanted exposure time to prosthetic-related complications.

7.3.1.2. Diagnostic Testing—Changing Signs or Symptoms

TTE is indicated in patients with primary MR (stages B to D) to evaluate the mitral valve apparatus and LV function after a change in signs or symptoms. The onset of symptoms (dyspnea on exertion, orthopnea, or declining exercise tolerance) is by itself a negative prognostic event even if LV function is preserved. Symptoms are the culmination of the pathophysiology of MR and may indicate changes in LV diastolic function, left atrial compliance, LV filling pressure and/or increases in pulmonary artery pressure, and decreases in RV function or the coexistence of TR. Therefore, symptoms add pathophysiological data not readily available from imaging. Further, there is no evidence that treatment with diuretics or other therapies that might relieve symptoms changes the prognostic effect of symptom onset. Once symptoms have occurred, the patient should be considered for mitral valve operation even if medication has led to improvement. Repeat TTE at the time of symptom onset is indicated to confirm that symptoms are likely due to MR or its effect on the left ventricle, which in turn supports surgical correction. The new onset of AF is also an indication for repeat TTE to look for changes in severity of MR and the status of the left ventricle.

Supporting References: (365, 376)

7.3.1.3. Diagnostic Testing—Routine Follow-Up

TTE should be performed on an annual or semiannual basis for surveillance of LV function (estimated by LVEF and end-systolic dimension) and pulmonary artery pressure in asymptomatic patients with severe *primary* MR (stage C1). Chronic severe MR is tolerated poorly, reaching a trigger for surgery at an average rate of about 8% per year. Because this progression varies from patient to patient and because prognosis worsens if correction of MR is delayed beyond the onset of these triggers, either referral to a Heart Valve Center of Excellence for early repair or very careful surveillance is mandatory. If a watchful waiting approach is pursued, periodic TTE is

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critical to examine the patient for changes in LV function and pulmonary pressure in determining the proper timing of surgery. For patients approaching the above benchmarks, semiannual TTE is recommended. It should be noted that echocardiographic measurements are variable, and management decisions that rest on these measurements should be confirmed by repeat TTE if the patient is approaching or has reached the important triggers for surgery noted above.

In patients with chronic *primary* MR that is less than severe (stages A and B), TTE is indicated periodically to evaluate for changes in MR severity. MR is a progressive disease. The LV volume overload induced by chronic *primary* MR causes eccentric cardiac remodeling with progressively increasing chamber volume, tending to reduce valve leaflet coaptation. Advancing valve pathology leads to further worsening of MR. This process may develop slowly without dramatic changes in symptoms or physical examination. Thus, MR could become severe and even lead to LV dysfunction without the patient or clinician being aware of it. Accordingly, periodic repeat TTE to examine for changes in severity of MR and LV size and function when baseline disease is less than severe is advisable. For mild MR, follow-up every 3 to 5 years is adequate unless the results of the physical examination or symptoms change. For moderate MR, follow-up every 1 to 2 years is recommended, again unless clinical status suggests a worsening in severity (Table 4).

Supporting Reference: (39)

7.3.1.4. Diagnostic Testing—Cardiac Catheterization

Left ventriculography and/or hemodynamic measurements are indicated when clinical assessment and/or noninvasive tests are inconclusive or discordant regarding 1) severity of MR, 2) LV function, or 3) the need for surgery. Imaging with these techniques is adequate for evaluation of MR in the majority of cases. However, invasive hemodynamic evaluation may be necessary in some cases, especially when there is a clinical discrepancy between symptomatic status and noninvasive testing. Elevated filling pressures support a cardiac cause for dyspnea and/or may indicate severely abnormal pathophysiology even when the patient claims to be asymptomatic. Conversely, a normal invasive hemodynamic examination in a symptomatic patient with what appears to be less than severe MR suggests a noncardiac cause for the symptoms. Hemodynamic evaluation can be especially helpful in patients with concomitant lung disease. Normal left atrial (or wedge) pressure and a large transpulmonary gradient suggest pulmonary hypertension due to lung disease rather than mitral valve disease. Patients usually complain of dyspnea with exertion, yet noninvasive evaluation is usually made at rest. Hemodynamic measurement made during either handgrip or dynamic exercise may be very revealing. Increased load with exercise may bring out severely disordered hemodynamics explaining the patient's exercise-related symptoms. Left ventriculography may also be of diagnostic benefit. Whereas echo-Doppler interrogation of the mitral valve measures flow velocity, ventriculography uses the density of contrast to determine the amount of blood flow from the left ventricle to LA. Although only semiquantitative, a carefully performed ventriculogram can add significantly to the diagnostic data pool.

Supporting Reference: (42)

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7.3.1.5. Diagnostic Testing—Exercise Testing: Recommendations

Class IIa

1. **Exercise hemodynamics with either Doppler echocardiography or cardiac catheterization is reasonable in symptomatic patients with chronic primary MR where there is a discrepancy between symptoms and the severity of MR at rest (stages B and C) (377, 378). *(Level of Evidence: B)***

The symptoms of chronic primary MR usually occur during exercise. Thus, evaluation during exercise may be very informative when resting TTE and symptomatic status are discordant or when the magnitude of LV and LA enlargement seem out of proportion to the severity of resting MR. In such cases, severity of MR and/or pulmonary artery pressure may increase during exercise, both helping to explain exercise-induced symptoms and indicating that mitral surgery may be in order. The change in pulmonary artery wedge pressure and LV diastolic pressure during exercise can be obtained during cardiac catheterization, which may further aid in determining the etiology of symptoms.

Supporting References: (42, 377, 378)

Class IIa

2. **Exercise treadmill testing can be useful in patients with chronic primary MR to establish symptom status and exercise tolerance (stages B and C). *(Level of Evidence: C)***

The onset of symptoms represents a key development in severe MR. However, some patients may not recognize their symptoms, may deny them, or may alter their lifestyle to remain asymptomatic. A formal treadmill exercise test can establish true exercise tolerance and can also form the baseline for future symptom assessment. Additional information about a cardiac or noncardiac limitation can be obtained using oxygen consumption measurements during exercise. Exercise echocardiography may add additional prognostic value beyond conventional exercise treadmill testing in patients with asymptomatic moderate or severe chronic primary MR.

Supporting References: (378-381)

7.3.2. Medical Therapy: Recommendations

Class IIa

1. **Medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR (stage D) and LVEF less than 60% in whom surgery is not contemplated (382-386). *(Level of Evidence: B)***

Patients with MR and LV dysfunction experience myocardial damage and HF. With onset of LV systolic dysfunction, surgery is usually indicated. However, in those patients in whom surgery is not performed or will be delayed, medical therapy for systolic dysfunction should be implemented. Although there are sparse data available specific to patients with MR with LV dysfunction, it seems reasonable to treat such patients with the standard regimen for HF, including beta-adrenergic blockade, ACE inhibitors or ARBs, and possibly aldosterone antagonists. Perhaps the best data exist for the use of beta blockers, which reverse LV dysfunction

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in experimental MR. Patients who are receiving beta blockers may have better surgical outcomes and delayed onset of LV dysfunction compared with those not taking these medications. ACE inhibition has not been effective in experimental MR with LV dysfunction but has caused reverse remodeling in a study with a small number of patients. Because aldosterone antagonism is thought to work in part by inhibiting fibrosis, its role in MR where little fibrosis occurs is unclear.

Supporting References: (382-386)

Class III: No Benefit

1. **Vasodilator therapy is not indicated for normotensive asymptomatic patients with chronic primary MR (stages B and C1) and normal systolic LV function (386-391). *(Level of Evidence: B)***

Because vasodilator therapy appears to be effective in acute severe symptomatic MR, it seems reasonable to attempt afterload reduction in chronic asymptomatic MR with normal LV function in an effort to forestall the need for surgery. However, the results from the limited number of trials addressing this therapy have been disappointing, demonstrating little or no clinically important benefit. Conversely, because vasodilators decrease LV size and mitral closing force, they may increase mitral valve prolapse, worsening rather than decreasing severity of MR. The foregoing does not apply to patients with concomitant hypertension. Hypertension must be treated because of the well-known morbidity and mortality associated with that condition and because increased LV systolic pressure by itself increases the systolic transmitral gradient and worsens severity of MR.

Supporting References: (386-391)

7.3.3. Intervention: Recommendations

See Table 17 for a summary of recommendations from this section.

Table 17. Summary of Recommendations for Chronic *Primary* MR

Recommendations	COR	LOE	References
MV surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF >30%	I	B	(365, 376)
MV surgery is recommended for asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30%–60% and/or LVESD ≥40 mm, stage C2)	I	B	(359-362, 392-394)
MV repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet	I	B	(87, 364, 395-409)
MV repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished	I	B	(86, 407-413)
Concomitant MV repair or replacement is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications	I	B	(414)
MV repair is reasonable in asymptomatic patients with chronic severe primary MR (stage C1) with preserved LV function (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1% when performed at a Heart Valve Center of Excellence	IIa	B	(39, 86, 415-419)
MV repair is reasonable for asymptomatic patients with chronic severe	IIa	B	(363, 415,

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nonrheumatic primary MR (stage C1) and preserved LV function in whom there is a high likelihood of a successful and durable repair with 1) new onset of AF or 2) resting pulmonary hypertension (PA systolic arterial pressure >50 mm Hg)			420-425)
Concomitant MV repair is reasonable in patients with chronic moderate primary MR (stage B) undergoing cardiac surgery for other indications	IIa	C	N/A
MV surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF ≤30% (stage D)	IIb	C	N/A
MV repair may be considered in patients with rheumatic mitral valve disease when surgical treatment is indicated if a durable and successful repair is likely or if the reliability of long-term anticoagulation management is questionable	IIb	B	(86, 406, 413)
Transcatheter MV repair may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe primary MR (stage D) who have a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities	IIb	B	(426)
MVR should not be performed for treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless MV repair has been attempted and was unsuccessful	III: Harm	B	(87, 407-409)

AF indicates atrial fibrillation; COR, Class of Recommendation; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; N/A, not applicable; NYHA, New York Heart Association; and PA, pulmonary artery.

Intervention for patients with primary MR consists of either surgical mitral valve repair or MVR. Mitral valve repair is preferred over MVR if a successful and durable repair can be achieved. Repair success is dependent on the mitral valve morphology as well as surgical expertise. Percutaneous mitral valve repair provides a less invasive alternative to surgery but is not approved for clinical use in the United States.

Supporting Reference: (426)

Class I

1. **Mitral valve surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF greater than 30% (365, 376). *(Level of Evidence: B)***

Primary MR is a mechanical problem of the leaflets that has only a mechanical solution—that of mitral valve surgery. The onset of symptoms that results from severe MR worsens prognosis even when LV function appears to be normal, and negative prognosis extends even to mild symptoms. Thus, the onset of symptoms is an indication for prompt mitral valve surgery.

Supporting References: (365, 376)

Class I

2. **Mitral valve surgery is recommended for asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30% to 60% and/or LVESD ≥40 mm, stage C2) (359-362, 392-394). *(Level of Evidence: B)***

The goal of therapy in MR is to correct it before the onset of LV systolic dysfunction and the subsequent adverse effect on patient outcomes. Ideally, mitral valve surgery should be performed when the patient's left ventricle approaches but has not yet reached the parameters that indicate systolic dysfunction (LVEF ≤60% or LVESD ≥40 mm). Because symptoms do not always coincide with LV dysfunction, imaging surveillance is

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used to plan surgery before severe dysfunction has occurred. If moderate LV dysfunction is already present, prognosis is reduced following mitral valve operation. Thus, further delay (even though symptoms are absent) will lead to greater LV dysfunction and a still worse prognosis. Because the loading conditions in MR allow continued late ejection into a lower-impedance LA, a higher cutoff for "normal" LVEF is used in MR than in other types of heart disease. Although it is clearly inadvisable to allow patients' LV function to deteriorate beyond the benchmarks of an LVEF ≤60% and/or LVESD ≥40 mm, some recovery of LV function can still occur even if these thresholds have been crossed.

Supporting References: (359-362, 392-394)

Class I

3. **Mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet (87, 364, 395-409). *(Level of Evidence: B)***

Mitral competence is only 1 function of the mitral valve apparatus. The mitral valve apparatus is an integral part of the left ventricle. It aids in LV contraction and helps maintain the efficient prolate ellipsoid shape of the left ventricle. Destruction of the mitral apparatus causes immediate LV dysfunction. Mitral valve repair is favored over MVR for 3 reasons:

1. Mitral valve repair is performed at a lower operative mortality rate than MVR. Although no RCTs exist, virtually every clinical report, including data from the STS database, indicates that operative risk (30-day mortality) for repair is about half that of MVR.
2. LV function is better preserved following repair preserving the integrity of the mitral valve apparatus versus following MVR.
3. Repair avoids the risks inherent to prosthetic heart valves, that is, thromboembolism or anticoagulant-induced hemorrhage for mechanical valves or structural deterioration for bioprosthetic valves.

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Because the success of repair increases with surgical volume and expertise, repair (which is the preferred treatment) is more likely to be accomplished in centers with surgeons who have expertise in this type of surgery. Mitral valve repair over MVR is indicated even in patients >65 years of age. When in doubt, MVR is preferable to a poor repair. The results of a minimally invasive approach performed via minithoracotomy/port access using direct vision, thoracoscopic, or robotic assistance versus a conventional sternotomy approach may be similar when performed by highly experienced surgeons.

Surgical repair of MR has been remarkably successful in the treatment of primary MR. When leaflet dysfunction is sufficiently limited so that only annuloplasty and repair of the posterior leaflet are necessary, repair of isolated degenerative mitral disease has led to outcomes distinctly superior to biological or mechanical valve replacement: an operative mortality of <1%; long-term survival equivalent to that of the age-matched general population; approximately 95% freedom from reoperation; and >80% freedom from recurrent moderate or severe (≥3+) MR at 15 to 20 years after operation. As much as one half of the posterior leaflet may be excised, plicated, or resuspended. Posterior leaflet repair has become sufficiently standardized so that valve

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repair rather than valve replacement is the standard of care in this situation. Execution of this procedure with a success rate ≥90% should be the expectation of every cardiac surgeon who performs mitral valve procedures. *Supporting References:* (87, 364, 395-409, 427-432)

Class I

4. **Mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished (86, 407-413). *(Level of Evidence: B)***

Degenerative mitral valve disease consisting of more than posterior leaflet disease requires a more complex and extensive repair. When the anterior leaflet or both leaflets require repair, durability of the repair is less certain, with a freedom from reoperation of approximately 80% and a freedom from recurrent moderate or severe MR of 60% at 15 to 20 years. These results are superior to the results of MVR, even in elderly patients. Repair should also be attempted if possible with other causes of severe MR, such as papillary muscle rupture, IE, and cleft mitral valve. As the repair becomes more complex, however, results of very complex repair in younger patients may be matched by results of durable mechanical MVR with careful management of anticoagulation.

More complex repair is not well standardized and is more surgically demanding. The Heart Valve Team should assign complex repairs to more experienced mitral valve surgeons with established outcomes, including acute success rate as well as long-term durability. The probability of mitral valve repair rather than MVR correlates with surgeon-specific mitral volumes. In a 2007 analysis, hospitals that performed <36 mitral operations per year had a 48% repair rate, whereas hospitals that performed >140 mitral operations per year had a 77% repair rate. Hospital mortality was also 50% lower, on average, in the highest-volume hospitals. There was, however, considerable overlap in specific hospital outcomes, with >25% of low-volume hospitals outperforming the median high-volume hospitals. This overlap suggests that hospital or surgeon-specific volumes should not be used as a surrogate for actual surgeon-specific repair rates and outcomes. *Supporting References:* (86, 407-413)

Class I

5. **Concomitant mitral valve repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications (414). *(Level of Evidence: B)***

During coronary revascularization and in cases of IE or other conditions where multiple valves may be involved, it is prudent to correct severe primary MR at the time of surgery. This is especially true when mitral repair can be performed in conjunction with AVR because operative risk is lower than that of double valve replacement. *Supporting Reference:* (414)

Class IIa

1. **Mitral valve repair is reasonable in asymptomatic patients with chronic severe primary MR (stage C1) with preserved LV function (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is greater than 95% with an**

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expected mortality rate of less than 1% when performed at a Heart Valve Center of Excellence (39, 86, 415-419). *(Level of Evidence: B)*

The onset of symptoms, LV dysfunction, or pulmonary hypertension worsens the prognosis for MR. Careful intensive surveillance may result in timing of valve surgery before these negative sequelae occur. However, an attractive alternative strategy for treating severe chronic primary MR is to perform early mitral repair before these triggers are reached. Early mitral repair avoids the need for intensive surveillance and also obviates the possibility that patients might become lost to follow-up or delay seeing their clinician until advanced LV dysfunction has already ensued. This strategy requires expertise in clinical evaluation and cardiac imaging to ensure that MR is severe. For this strategy to be effective, a durable repair must be provided. An unwanted valve replacement, exposing the patient to the unneeded risks accrued from prosthetic valve replacement, or a repair that fails, necessitating reoperation, should be considered complications of this approach. Thus, there must be a high degree of certainty that a durable repair can be performed. In this regard, posterior leaflet repair is usually more durable than anterior leaflet repair, especially in less experienced hands, and high surgical volume is also associated with better repair rates and more durable outcomes. These operations on the asymptomatic patient should be performed in Heart Valve Centers of Excellence by experienced surgeons with expertise in mitral valve repair. When performed by experienced surgeons in a Heart Valve Center of Excellence, there is a lower risk of patients developing HF and lower mortality rates in patients with severe MR from flail leaflets who undergo early operation as opposed to watchful waiting.

Supporting References: (39, 86, 415-419)

Class IIa

2. **Mitral valve repair is reasonable for asymptomatic patients with chronic severe nonrheumatic primary MR (stage C1) and preserved LV function (LVEF >60% and LVESD <40 mm) in whom there is a high likelihood of a successful and durable repair with 1) new onset of AF or 2) resting pulmonary hypertension (pulmonary artery systolic arterial pressure >50 mm Hg) (363, 415, 420-425). *(Level of Evidence: B)***

In nonrheumatic MR, the onset of AF is in part due to enlarging left atrial size, and its presence worsens surgical outcome. Furthermore, the longer AF is present, the more likely it is to persist. Thus, it may be reasonable to restore mitral competence by low-risk repair with the hope that the ensuing reduction in left atrial size will help restore and maintain sinus rhythm. However, restoration of sinus rhythm following valve surgery is uncertain, and concomitant AF ablation surgery may be warranted (Section 14.2.2). This strategy does not apply to rheumatic MR, where active atrial inflammation may make restoration of sinus rhythm less likely and valve scarring reduces the likelihood of a successful repair. The presence of pulmonary arterial hypertension due to MR is associated with poorer outcome after valve surgery. Thus, it is reasonable to consider surgery in these patients if there is a high likelihood of a successful and durable repair.

Supporting References: (363, 420-425)

Class IIa

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3. **Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B) when undergoing cardiac surgery for other indications. *(Level of Evidence: C)***

Because MR is a progressive lesion, it is reasonable to address it at the time of other cardiac surgery. This is especially true if the mitral valve can be repaired. However, the added risk of mitral valve surgery must be weighed against the potential for progression of MR. In such cases, increased operative mortality might not be justified in treating moderate MR.

Supporting Reference: (433)

Class IIb

1. **Mitral valve surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF less than or equal to 30% (stage D). *(Level of Evidence: C)***

Most patients with decompensated MR and an LVEF ≤30% have secondary rather than primary MR. However in the rare cases where valve pathology indicates a clear primary cause in a patient with far-advanced LV dysfunction, surgery might be beneficial, especially in patients without severe comorbidities. Repair seems reasonable in such patients because of the likelihood of continued deterioration in LV function if surgery is not performed. However, data regarding surgery in patients with primary MR and a low LVEF are lacking.

Class IIb

2. **Mitral valve repair may be considered in patients with rheumatic mitral valve disease when surgical treatment is indicated if a durable and successful repair is likely or when the reliability of long-term anticoagulation management is questionable (86, 406, 413). *(Level of Evidence: B)***

Rheumatic mitral valve disease is less suitable for mitral repair than complex degenerative disease. Durability of the repair is limited by thickened or calcified leaflets, extensive subvalvular disease with chordal fusion and shortening, and progression of rheumatic disease. Freedom from reoperation at 20 years, even in experienced hands, is in the 50% to 60% range. In a large series from Korea, repair was accomplished in 22% of patients operated on for rheumatic disease. One third of these patients who underwent repair had significant stenosis or regurgitation at 10 years. Repair of rheumatic mitral valve disease should be limited to patients with less advanced disease in whom a durable repair can be accomplished or to patients in whom a mechanical prosthesis cannot be used because of anticoagulation management concerns.

Supporting References: (434, 435)

Class IIb

3. **Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for HF (426). *(Level of Evidence: B)***

An RCT of percutaneous mitral valve repair using the MitraClip device versus surgical mitral repair was conducted in the United States. The clip was found to be safe but less effective than surgical repair because

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residual MR was more prevalent in the percutaneous group. However, the clip did reduce severity of MR, improved symptoms, and led to reverse LV remodeling. Percutaneous mitral valve repair should only be considered for patients with chronic primary MR who remain severely symptomatic with NYHA class III to IV HF symptoms despite optimal GDMT for HF and who are considered inoperable.

Supporting References: (426, 436, 437)

Class III: Harm

1. **MVR should not be performed for the treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless mitral valve repair has been attempted and was unsuccessful (87, 407-409). *(Level of Evidence: B)***

Surgical repair of MR has been remarkably successful, particularly in the treatment of chronic primary MR. Repair of isolated degenerative mitral disease, when leaflet dysfunction is sufficiently limited that only annuloplasty and repair of the posterior leaflet are necessary, has led to outcomes distinctly superior to biological or mechanical MVR; operative mortality of <1%; long-term survival equivalent to that of age-matched general population; approximately 95% freedom from reoperation; and >80% freedom from recurrent moderate or severe (≥3+) MR at 15 to 20 years after operation. As much as one half of the posterior leaflet may be excised, plicated, or resuspended. Posterior leaflet repair has become sufficiently standardized in this situation so that repair rather than MVR is the standard of care. Execution of this procedure with a success rate ≥90% should be the expectation of every cardiac surgeon who performs mitral valve procedures.

Supporting References: (87, 407-409)

See Online Data Supplements 16 and 17 for more information on intervention (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

7.4. Chronic Secondary MR

7.4.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **TTE is useful to establish the etiology of chronic secondary MR (stages B to D) and the extent and location of wall motion abnormalities and to assess global LV function, severity of MR, and magnitude of pulmonary hypertension. *(Level of Evidence: C)***

In general, the presence of chronic secondary MR worsens the prognosis of patients with LV systolic dysfunction and symptoms of HF, and most patients with secondary MR have severe global LV dysfunction. However, in some patients, a limited but strategically placed wall motion abnormality may also cause chronic secondary MR, and prognosis may be better in such patients. An initial TTE helps establish the cause of chronic secondary MR and also serves as a baseline for future comparisons. In patients with secondary MR, outcome studies have shown poorer prognosis with effective regurgitant orifice ≥20 mm^2. It is recognized that there is difficulty assessing secondary MR in patients with reduced LV systolic function and low forward flow.

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Supporting References: (438, 439)

Class I

2. **Noninvasive imaging (stress nuclear/positron emission tomography, CMR, or stress echocardiography), cardiac CT angiography, or cardiac catheterization, including coronary arteriography, is useful to establish etiology of chronic secondary MR (stages B to D) and/or to assess myocardial viability, which in turn may influence management of functional MR. *(Level of Evidence: C)***

Prognosis is poor for both ischemic and nonischemic MR, but ischemic MR lends itself to the possibility of revascularization and potential improvement in LV function if CAD has led to large areas of hibernating viable myocardium. CT angiography is usually adequate to rule out significant CAD and thus rule out ischemic MR. If CAD is detected and noninvasive testing demonstrates areas of viability, coronary arteriography is pursued to better define the anatomy for potential revascularization.

Supporting Reference: (440)

7.4.2. Medical Therapy: Recommendations

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Class I

1. **Patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated (310, 441-445). *(Level of Evidence: A)***

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Chronic secondary MR usually develops as a result of severe LV dysfunction. Thus, standard GDMT for HF forms the mainstay of therapy. Diuretics, beta blockers, ACE inhibition or ARBs, and aldosterone antagonists help improve symptoms and/or prolong life in HF in general and probably do so even when HF is complicated by chronic secondary MR.

Supporting References: (310, 441-445)

Class I

2. **Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy (446, 447). *(Level of Evidence: A)***

Wall motion abnormalities are a common cause of chronic secondary MR, and their presence worsens the condition. The presence of conduction system abnormalities, especially left bundle-branch block, causes disordered LV contraction that exacerbates or is the primary cause of wall motion abnormalities. Electrical resynchronization may reduce or even eliminate wall motion abnormalities. Cardiac resynchronization therapy may also improve LV function and mitral valve closing force, which in turn leads to a reduction in chronic secondary MR in some cases. Thus, cardiac resynchronization therapy should be considered in symptomatic patients with chronic secondary MR who meet the indications for device therapy as outlined in the ACC/AHA guidelines for device-based therapy.

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Supporting References: (446, 447)

7.4.3. Intervention: Recommendations

See Table 18 for a summary of recommendations for this section and Figure 4 for indications for surgery for MR.

Table 18. Summary of Recommendations for Chronic Severe Secondary MR

Recommendations	COR	LOE	References
MV surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR	IIa	C	N/A
MV surgery may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe secondary MR (stage D)	IIb	B	(439, 448-458)
MV repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery	IIb	C	N/A

AVR indicates aortic valve replacement; CABG, coronary artery bypass graft; COR, Class of Recommendation; LOE, Level of Evidence; MR, mitral regurgitation; MV, mitral valve; N/A, not applicable; and NYHA, New York Heart Association.

Chronic severe *secondary* MR adds volume overload to a decompensated left ventricle and worsens prognosis. However, there are sparse data that correcting MR prolongs life or even improves symptoms over an extended time. The benefits of performing mitral valve repair over MVR are also unclear in this subset of patients. Percutaneous mitral valve repair provides a less invasive alternative to surgery but is not approved for clinical use in the United States.

Supporting References: (426, 436, 459)

Class IIa

1. **Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR. *(Level of Evidence: C)***

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There is no proof that correction of chronic secondary MR at the time of AVR or CABG is effective in prolonging life or relieving symptoms, but it seems wise to address the mitral valve during those operations. Although it may be hoped that the revascularization will recruit hibernating myocardium and reduce chronic secondary MR or that LV pressure reduction from relief of AS or volume reduction from relief of AR might improve chronic secondary MR, such hopes may not be realized. Failing to correct chronic secondary MR may leave the patient with severe residual MR.

Class IIb

1. **Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF (439, 448-458). *(Level of Evidence: B)***

Although it is clear that chronic severe secondary MR adds to the burden of HF by imposing volume overload on an already compromised left ventricle and worsens prognosis, there is remarkably little evidence that correcting chronic severe secondary MR prolongs life or even improves symptoms for a prolonged period. This paradox may result from the fact that mitral surgery in ischemic MR does not prevent CAD from progressing,

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nor does it prevent the continued idiopathic myocardial deterioration in nonischemic chronic secondary MR. Furthermore, when chronic severe secondary MR is addressed surgically, it is not clear that repair, so valuable in treating primary MR, is even preferred over MVR in chronic severe secondary MR. Small RCTs have demonstrated that mitral valve surgery reduces chamber size and improves peak oxygen consumption in chronic severe secondary MR. Deciding which patients with chronic severe secondary MR will benefit from mitral surgery awaits the results of larger RCTs. Ischemic or dilated cardiomyopathy presents different challenges for mitral repair. Regurgitation is caused by annular dilation as well as apical and lateral displacement of the papillary muscles. New techniques have facilitated mitral repair in this situation, but durability of the repair is primarily dependent on regression or progression of ventricular dilation. If the heart continues to dilate, long-term durability of the repair is moot; the survival of the patient is limited.

Supporting References: (434, 435, 439, 448-458)

Class IIb

2. **Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery.** ***(Level of Evidence: C)***

Because MR tends to be a progressive disease, it may be helpful to address moderate MR when other cardiac surgery is being performed. Because adding MVR to other valve surgery increases surgical risk, it seems logical that repair would be preferred in such instances; however, there are sparse data available at the time of publication to support this concept.

Supporting Reference: (433)

See Online Data Supplement 18 for more information on intervention (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Figure 4. Indications for Surgery for MR

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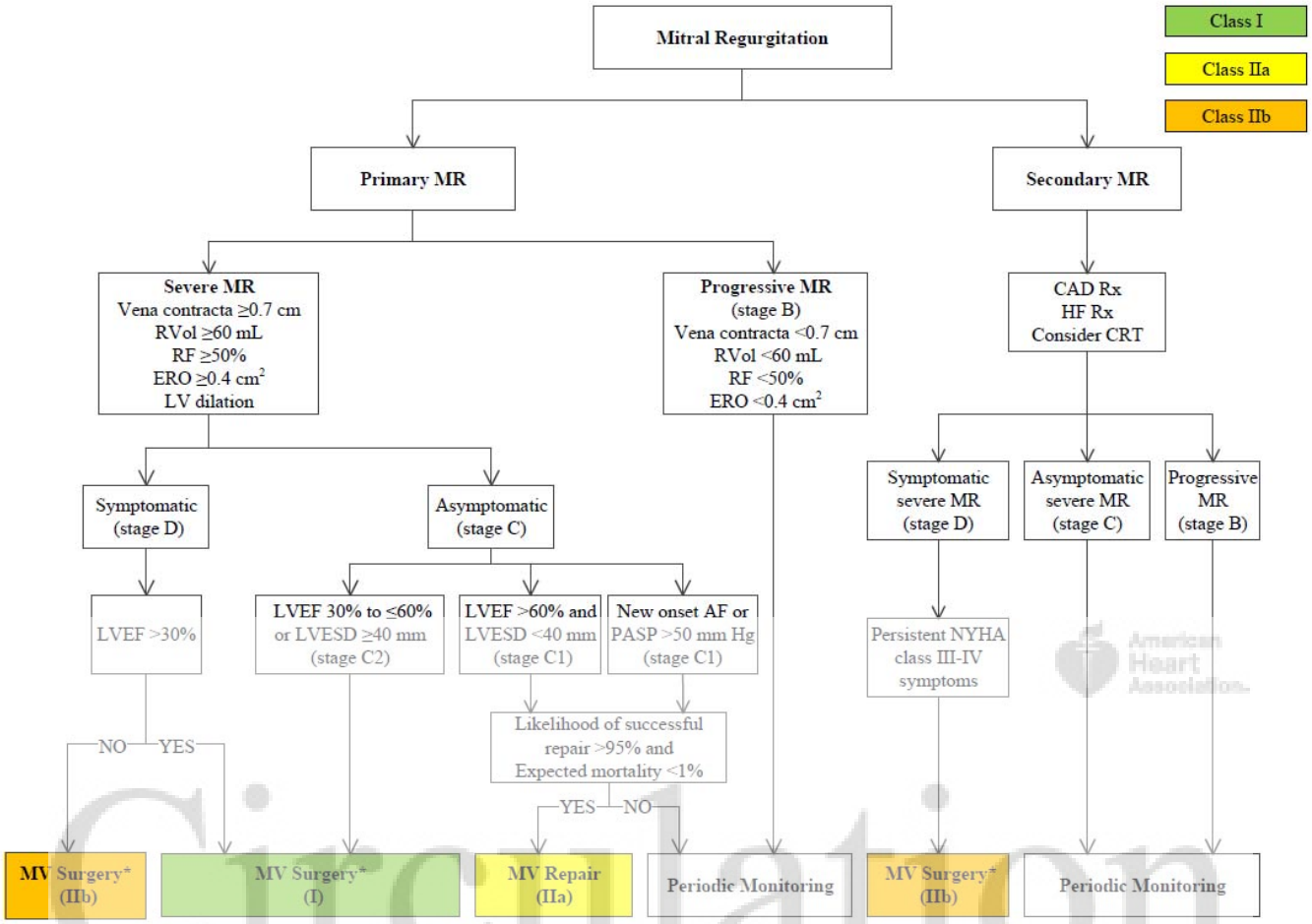

*Mitral valve repair is preferred over MVR when possible.

AF indicates atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy.

8. Tricuspid Valve Disease

8.1. Stages of TR

Trace-to-mild degrees of TR of no physiological consequence are commonly detected on TTE in subjects with anatomically normal valves. *Primary* disorders of the tricuspid apparatus that can lead to more significant degrees of TR include rheumatic disease, prolapse, congenital disease (Ebstein's), IE, radiation, carcinoid, blunt chest wall trauma, RV endomyocardial biopsy–related trauma, and intra-annular RV pacemaker or implantable cardioverter-defibrillator leads. Approximately 80% of cases of significant TR are *functional* in nature and related to tricuspid annular dilation and leaflet tethering in the setting of RV remodeling due to pressure and/or volume overload. The tricuspid annulus is a saddle-shaped ellipsoid that becomes planar and circular as it dilates in an anterior-posterior direction and will often not return to its normal size and configuration after relief of RV overload. Table 19 shows the stages (A through D) of *primary* and *functional* TR as defined for other valve

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lesions. Severe TR (stages C and D) is associated with poor prognosis independent of age, LV and RV function, and RV size. Patients with signs or symptoms of right HF would fit into the stage D category even if they do not meet other hemodynamic or morphological criteria.

Supporting Reference: (460)

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Table 19. Stages of TR

Stage	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	At risk of TR	**Primary** • Mild rheumatic change • Mild prolapse • Other (e.g., IE with vegetation, early carcinoid deposition, radiation) • Intra-annular RV pacemaker or ICD lead • Postcardiac transplant (biopsy related) **Functional** • Normal • Early annular dilation	• No or trace TR	• None	• None or in relation to other left heart or pulmonary/pulmonary vascular disease
B	Progressive TR	**Primary** • Progressive leaflet deterioration/destruction • Moderate-to-severe prolapse, limited chordal rupture **Functional** • Early annular dilation • Moderate leaflet tethering	**Mild TR** • Central jet area <5.0 cm^2 • Vena contracta width not defined • CW jet density and contour: soft and parabolic • Hepatic vein flow: systolic dominance **Moderate TR** • Central jet area 5–10 cm^2 • Vena contracta width not defined but <0.70 cm • CW jet density and contour: dense, variable contour • Hepatic vein flow: systolic blunting	**Mild TR** • RV/RA/IVC size normal **Moderate TR** • No RV enlargement • No or mild RA enlargement • No or mild IVC enlargement with normal respirophasic variation • Normal RA pressure	• None or in relation to other left heart or pulmonary/pulmonary vascular disease
C	Asymptomatic, severe TR	**Primary** • Flail or grossly distorted leaflets **Functional** • Severe annular dilation	• Central jet area >10.0 cm^2 • Vena contracta width >0.7 cm • CW jet density and contour: dense, triangular with early peak • Hepatic vein flow: systolic	• RV/RA/IVC dilated with decreased IVC respirophasic variation • Elevated RA pressure with "c-V" wave • Diastolic interventricular	• None, or in relation to other left heart or pulmonary/pulmonary vascular disease

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		(>40 mm or 21 mm/m^2) • Marked leaflet tethering	reversal	septal flattening may be present	
D	Symptomatic severe TR	**Primary** • Flail or grossly distorted leaflets **Functional** • Severe annular dilation (>40 mm or >21 mm/m^2) • Marked leaflet tethering	• Central jet area >10.0 cm^2 • Vena contracta width >0.70 cm • CW jet density and contour: dense, triangular with early peak • Hepatic vein flow: systolic reversal	• RV/RA/IVC dilated with decreased IVC respirophasic variation • Elevated RA pressure with "c-V" wave • Diastolic interventricular septal flattening • Reduced RV systolic function in late phase	• Fatigue, palpitations, dyspnea, abdominal bloating, anorexia, edema

*Several valve hemodynamic criteria are provided for assessment of severity of TR, but not all criteria for each category will necessarily be present in every patient. Categorization of severity of TR as mild, moderate, or severe also depends on image quality and integration of these parameters with clinical findings.

CW indicates continuous wave; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; and TR, tricuspid regurgitation.

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8.2. Tricuspid Regurgitation

See Figure 5 (Section 8.2.3) for indications for surgery**.**

8.2.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **TTE is indicated to evaluate severity of TR, determine etiology, measure sizes of right-sided chambers and inferior vena cava, assess RV systolic function, estimate pulmonary artery systolic pressure, and characterize any associated left-sided heart disease. (*Level of Evidence: C)***

Most TR is clinically silent. Advanced degrees of TR may be detected on physical examination by the appearance of elevated "c-V" waves in the jugular venous pulse, a systolic murmur at the lower sternal border that increases in intensity with inspiration, and a pulsatile liver edge. In many patients, characteristic findings in the jugular venous pulse are the only clues to the presence of advanced TR, because a murmur may be inaudible even with severe TR. Symptoms include fatigue from low cardiac output, abdominal fullness, edema, and palpitations, particularly if AF is also present. Progressive hepatic dysfunction may occur due to the elevated right atrial pressure, and thus assessment of liver function is useful in patients with advanced degrees of TR.

TTE can distinguish primary from functional TR, define any associated left-sided valvular and/or myocardial disease, and provide an estimate of pulmonary artery systolic pressure. Characterization of severity of TR (Table 19) relies on an integrative assessment of multiple parameters as recommended by the ASE and EAE. In cases of functional TR, the tricuspid annular diameter should be measured in the apical 4-chamber view. There is a linear relationship between annular diameter and tricuspid regurgitant volume. A diastolic diameter >40 mm (or >21 mm/m^2) indicates significant annular dilation and an increased risk of persistent or progressive TR after isolated mitral valve surgery. With RV remodeling, tricuspid valve leaflet tethering height and area also contribute to functional TR and may predict the need for repair techniques other than annuloplasty to achieve an effective and durable operative result. Pulmonary artery systolic pressure is estimated from the maximal tricuspid valve regurgitant velocity using the modified Bernoulli equation. The accuracy of this technique can be compromised in severe TR due to the difficulty in assessing right atrial pressure as well as potential inaccuracies of applying the simplified Bernoulli equation to lesions with laminar flow. Assessment of RV systolic function is challenged by geometric and image acquisition constraints, as well as by variability in RV loading conditions. Normal RV systolic function is defined by several parameters, including tricuspid annular plane systolic excursion >16 mm, tricuspid valve annular velocity (S') >10.0 cm per second, and RV end-systolic area <20.0 cm^2 or fractional area change >35%. TEE for tricuspid valve assessment can be considered when TTE images are inadequate, although visualization of the tricuspid valve with TEE can also be suboptimal.

Supporting References: (5, 461-469, 469-471)

Class IIa

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1. **Invasive measurement of pulmonary artery pressures and pulmonary vascular resistance can be useful in patients with TR when clinical and noninvasive data regarding their values are discordant.** ***(Level of Evidence: C)***

When physical examination, ECG, and TTE data regarding estimated pulmonary artery systolic pressure are either discordant or insufficient, including when the TR jet velocity signal is inadequate or may underestimate pulmonary artery systolic pressure, invasive measurement of pulmonary artery pressures and pulmonary vascular resistance can be helpful to guide clinical decision making in individual patients. Invasive data are essential for accurate diagnosis of the cause of pulmonary hypertension and for the assessment of pulmonary vascular reactivity following vasodilator challenge. Direct measurements of right atrial pressure may also be useful for clinical decision making. Right ventriculography may further aid in the evaluation of the severity of TR and the status of the right ventricle. Thermodilution cardiac output measurements may be inaccurate with severe TR, and thus a Fick cardiac output should be measured to apply to the calculation of pulmonary resistance.

Class IIb

1. **CMR or real-time 3D echocardiography may be considered for assessment of RV systolic function and systolic and diastolic volumes in patients with severe TR (stages C and D) and suboptimal 2D echocardiograms.** ***(Level of Evidence: C)***

Assessment of RV systolic function in patients with TR is a critical component of preoperative planning, especially in the context of reoperative isolated tricuspid valve repair or replacement years after left-sided valve surgery. Impaired RV systolic function negatively impacts early functional, late functional, and survival outcomes following tricuspid valve surgery. Evaluation with TTE or TEE may be suboptimal in some patients, due to poor acoustic windows, the technical limitations of standard echocardiographic and Doppler techniques, and dynamic changes in RV loading conditions. Both CMR and real-time 3D echocardiography may provide more accurate assessment of RV volumes and systolic function, as well as annular dimension and the degree of leaflet tethering. CMR may be the ideal modality in young asymptomatic patients with severe TR to assess initial and serial measurements of RV size and systolic function. In addition, echocardiographic strain imaging or CT scanning may be useful in assessing RV function. These imaging modalities are not widely used at the time of guideline publication, and outcome data are needed to determine the incremental utility of these tests. *Supporting References:* (472-481)

Class IIb

2. **Exercise testing may be considered for the assessment of exercise capacity in patients with severe TR with no or minimal symptoms (stage C).** ***(Level of Evidence: C)***

Patients with severe functional TR usually report symptoms referable to the responsible left-sided valve or myocardial abnormality. However, in some patients with primary TR, symptoms may not emerge until relatively late in the course of the disease. As is the case for left-sided valve lesions, treadmill or bicycle testing may

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uncover limitations to exercise not previously recognized by the patient and prompt earlier evaluation for surgery. Although some clinical experience has been reported for patients with Ebstein's anomaly, the effect on clinical outcomes of any exercise-induced changes in RV size/function or pulmonary artery pressures in patients with severe TR (stage C) has not been prospectively studied.

Supporting Reference: (482)

8.2.2. Medical Therapy: Recommendations

Class IIa

1. **Diuretics can be useful for patients with severe TR and signs of right-sided HF (stage D).** ***(Level of Evidence: C)***

Patients with severe TR usually present with signs or symptoms of right HF, including peripheral edema and ascites. Diuretics can be used to decrease volume overload in these patients. Loop diuretics are typically provided and may relieve systemic congestion, but their use can be limited by worsening low-flow syndrome. Aldosterone antagonists may be of additive benefit, especially in the setting of hepatic congestion, which may promote secondary hyperaldosteronism.

Class IIb

1. **Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional TR (stages C and D).** ***(Level of Evidence: C)***

Medical therapies for management of severe TR (stages C and D) are limited. Attention should be focused on the causative lesion in patients with functional TR. Reduction of pulmonary artery pressures and pulmonary vascular resistance with specific pulmonary vasodilators may be helpful to reduce RV afterload and functional TR in selected patients with pulmonary hypertension who demonstrate acute responsiveness during invasive testing. Medical treatment of conditions that elevate left-sided filling pressures, such as systemic hypertension, should be optimized.

Supporting References: (483, 484)

8.2.3. Intervention: Recommendations

Class I

1. **Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery.** ***(Level of Evidence: C)***

The indications for surgical correction of TR are most often considered at the time of mitral or aortic valve surgery. Severe TR of either a primary or functional nature may not predictably improve after treatment of the left-sided valve lesion and reduction of RV afterload; as such, severe TR should be addressed as part of the index procedure. Reoperation for severe, isolated TR after left-sided valve surgery is associated with a perioperative mortality rate of 10% to 25%. Tricuspid valve repair does not add appreciably to the risks of

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surgery and can be accomplished with a clinically insignificant increase in ischemic time. There has been a significant increase in the number of tricuspid valve repairs performed for this indication over the past decade. Tricuspid valve repair is preferable to replacement. When replacement is necessary for primary, uncorrectable tricuspid valve disease, the choice of prosthesis is individualized, with the usual trade-offs between thrombosis/anticoagulation with a mechanical valve and durability with a tissue valve. Meta-analysis has shown no difference in overall survival between mechanical and tissue valves for patients undergoing tricuspid valve replacement. The risks and benefits of tricuspid valve operation should be carefully considered in the presence of severe RV systolic dysfunction or irreversible pulmonary hypertension, due to the possibility of RV failure after operation.

Supporting References: (485-494)

Class IIa

1. **Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at the time of left-sided valve surgery with either 1) tricuspid annular dilation or 2) prior evidence of right HF (464-466, 495-501). *(Level of Evidence: B)***

Left uncorrected at the time of left-sided valve surgery, mild or moderate degrees of functional TR may progress over time in approximately 25% of patients and result in reduced long-term functional outcome and survival. Risk factors for persistence and/or progression of TR include tricuspid annulus dilation (>40 mm diameter or 21 mm/m^2 diameter indexed to body surface area on preoperative TTE; >70 mm diameter on direct intraoperative measurement); degree of RV dysfunction/remodeling; leaflet tethering height; pulmonary artery hypertension; AF; nonmyxomatous etiology of MR; and intra-annular RV pacemaker or implantable cardioverter-defibrillator leads. The cut-off of >70 mm diameter on direct intraoperative measurement originated from a single center, performed with the patient on cardiopulmonary bypass using a supple ruler, taken from the anteroseptal commissure to the anteroposterior commissure. Echocardiography is usually performed on the beating heart and examines a different plane of the tricuspid annulus. Numerous observational studies and 1 prospective RCT attest to the benefit on several echocardiographic and functional parameters of tricuspid repair at the time of mitral valve surgery for mild-to-moderate TR (stage B) with tricuspid annulus dilation. When surgery is performed for isolated severe primary MR due to a degenerative etiology, less than moderate TR is unlikely to progress if left untreated. A prior recent history of right HF is also an indication for tricuspid valve repair at the time of left-sided valve surgery. A survival benefit with tricuspid repair in this setting has not been demonstrated. Management of indwelling pacemaker or implantable cardioverter-defibrillator leads may require their removal with epicardial placement in selected patients. Other approaches, such as sequestering the leads in a commissure or placing them in an extra-annular position, may be used. Following repair with ring annuloplasty, residual TR is present in approximately 10% of patients at 5 years.

Supporting References: (463-466, 495-504)

Class IIa

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2. **Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (stage D).** ***(Level of Evidence: C)***

Correction of symptomatic severe primary TR (stage D) in patients without left-sided valve disease is preferentially performed before onset of significant RV dysfunction. Replacement may be required because of the extent and severity of the underlying pathology (e.g., carcinoid, radiation, Ebstein's anomaly). Reduction or elimination of the regurgitant volume load can alleviate systemic venous and hepatic congestion and decrease reliance on diuretics. Patients with severe congestive hepatopathy may also benefit from surgery to prevent irreversible cirrhosis of the liver. Quality and duration of long-term survival are related to residual RV function.

Class IIb

1. **Tricuspid valve repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery.** ***(Level of Evidence: C)***

When pulmonary artery hypertension is caused predominantly by left-sided valve disease, effective surgery on the left-sided valve lesions usually leads to a fall in RV afterload and improvement in functional TR, especially in the absence of significant (i.e., >40 mm on TEE) tricuspid annulus dilation. This observation dates to the early years of mitral valve surgery. Prediction rules that account for the relative contributions of pulmonary hypertension and only mild-to-moderate degrees of tricuspid annulus enlargement for the risk of progressive TR are lacking. The benefit of routine tricuspid valve repair in this context is less clear across broad populations but may be considered on an individual basis.

Supporting References: (503, 505, 506)

Class IIb

2. **Tricuspid valve surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction.** ***(Level of Evidence: C)***

The optimal timing of tricuspid valve surgery for asymptomatic or minimally symptomatic, severe primary TR has not been established. Extrapolation from limited experiences reported for patients with stable carcinoid heart disease and patients with a flail tricuspid leaflet and application of the management principles adopted for patients with severe MR suggest that serial assessments of RV size and function might trigger consideration of corrective surgery in selected patients with severe, primary TR when a pattern of continued deterioration can be established and the risks of surgery are considered acceptable. In otherwise healthy patients without other comorbidities, such as the patient with severe TR due to trauma, the risk of tricuspid valve operation is low (<1% to 2%) in the absence of RV dysfunction or pulmonary hypertension.

Supporting References: (507, 508)

Class IIb

3. **Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms due to severe TR (stage D) in patients who have undergone previous left-sided valve**

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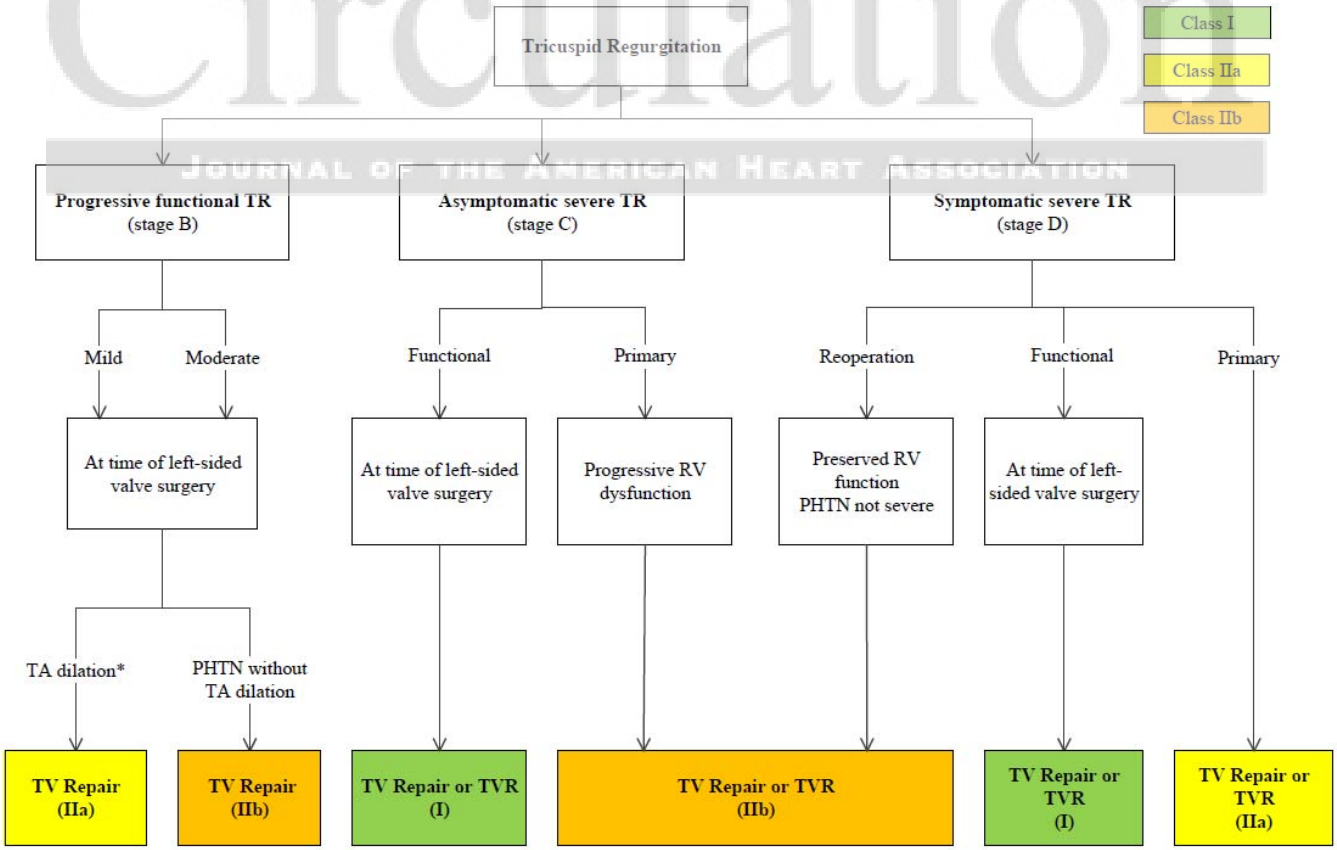
surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction. ***(Level of Evidence: C)***

Isolated tricuspid valve surgery for severe TR has historically been performed relatively late in the natural history of the disease and once patients have become symptomatic with signs of right HF. Unadjusted mortality rates for isolated tricuspid valve surgery have therefore exceeded those reported for isolated aortic or mitral valve surgery, and this trend has been even more pronounced following reoperative tricuspid surgery late after left-sided valve surgery. This high mortality is likely related to the advanced nature of RV failure encountered at the time of the second procedure, residual pulmonary hypertension, LV dysfunction, and other valve abnormalities. Two Heart Valve Centers of Excellence have reported perioperative mortality rates with tricuspid valve reoperation of 4.2% and 13.2%, respectively. Thus, the hazards imposed by reoperation have influenced decision making for repair of functional TR initially at the time of left-sided valve surgery. The sobering results seen with tricuspid valve repair at reoperation inject a note of caution into the recommendations for its performance and may encourage replacement with an age-appropriate (mechanical or biological) prosthesis. The presence of either severe and uncorrectable pulmonary hypertension or significant RV dysfunction constitutes a relative contraindication to reoperation.

Supporting References: (485-489, 509-512)

Figure 5. Indications for Surgery



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*See Table 19 for definition of stages. TA dilation is defined by >40 mm on TTE (>21 mm/m^2) or >70 mm on direct intraoperative measurement.
LV indicates left ventricular; PHTN, pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; TV, tricuspid valve; and TVR, tricuspid valve replacement.

See Online Data Supplement 19 for more information on outcomes following tricuspid valve surgery (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

8.3. Stages of Tricuspid Stenosis

See Table 20 for the stages of severe tricuspid stenosis (TS).

Table 20. Stages of Severe TS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
C, D	Severe TS	• Thickened, distorted, calcified leaflets	• T ½ ≥190 ms • Valve area ≤1.0 cm^2	• RA/IVC enlargement	• None or variable and dependent on severity of associated valve disease and degree of obstruction

The transtricuspid diastolic gradient is highly variable and is affected by heart rate, forward flow, and phases of the respiratory cycle. However, severe TS usually has mean pressure gradients >5 to 10 mm Hg at heart rate 70.

IVC indicates inferior vena cava; RA, right atrium; T ½, pressure half-time; and TS, tricuspid stenosis. (8)

8.4. Tricuspid Stenosis

8.4.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **TTE is indicated in patients with TS to assess the anatomy of the valve complex, evaluate severity of stenosis, and characterize any associated regurgitation and/or left-sided valve disease. *(Level of Evidence: C)***

Rheumatic disease is the most common etiology of TS. Its clinical manifestations are far overshadowed by those attributable to the associated left-sided (particularly mitral) valve disease. Because TS is often not detected during bedside examination, TTE is essential for diagnosis and characterization. TS is usually accompanied by TR of varying severity. When valve and/or chordal thickening and calcification are evident, additional findings indicative of severe TS include mean pressure gradient >5 mm Hg, pressure half-time ≥190 milliseconds, valve area ≤1.0 cm^2 (continuity equation), and associated right atrial and inferior vena cava enlargement. It is recognized that assessment of TS severity with TTE is limited by several technical factors; thus, these values are less well validated than those reported for MS.

Supporting Reference: (8)

Class IIb

1. **Invasive hemodynamic assessment of severity of TS may be considered in symptomatic patients when clinical and noninvasive data are discordant. *(Level of Evidence: C)***

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Hemodynamic assessment of TS is rarely undertaken for patients with acquired disease but may be performed in selected patients at the time of invasive study for another indication, such as MS with pulmonary hypertension. Direct assessment of the absolute right atrial and RV diastolic pressure may be useful in determining the contribution of TS to the patient's signs or symptoms.

8.4.2. Medical Therapy

As for patients with severe TR, loop diuretics may be useful to relieve systemic and hepatic congestion in patients with severe, symptomatic TS, although their use may be limited by worsening low-flow syndrome. Attention to left-sided valve disease and AF, when present, is also important.

8.4.3. Intervention: Recommendations

Class I

1. **Tricuspid valve surgery is recommended for patients with severe TS at the time of operation for left-sided valve disease.** ***(Level of Evidence: C)***

Surgery for severe TS is most often performed at the time of operation for left-sided valve disease, chiefly rheumatic MS/MR. If repair is not adequate or feasible due to valve destruction or multiple levels of pathological involvement, replacement may be necessary. The choice of prosthesis should be individualized. Perioperative mortality rates are higher for mitral plus tricuspid versus either isolated mitral or tricuspid surgery alone.

Supporting Reference: (489)

Class I

2. **Tricuspid valve surgery is recommended for patients with isolated, symptomatic severe TS.** ***(Level of Evidence: C)***

Relief of severe stenosis should lower elevated right atrial and systemic venous pressures and alleviate associated symptoms. Tricuspid valve surgery is preferred over percutaneous balloon tricuspid commissurotomy for treatment of symptomatic severe TS because most cases of severe TS are accompanied by TR (rheumatic, carcinoid, other), and percutaneous balloon tricuspid commissurotomy may either create or worsen regurgitation. There is also a relative lack of long-term follow-up data on patients managed with percutaneous balloon tricuspid commissurotomy for this indication. Outcomes with surgery are dependent on RV function.

Supporting References: (513, 514)

Class IIb

1. **Percutaneous balloon tricuspid commissurotomy might be considered in patients with isolated, symptomatic severe TS without accompanying TR.** ***(Level of Evidence: C)***

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Isolated, symptomatic severe TS without accompanying TR is an extremely rare condition for which percutaneous balloon tricuspid commissurotomy might be considered, recognizing its short-term limitations and the lack of long-term outcome data.

See Online Data Supplement 19 for more information on outcomes following tricuspid valve surgery (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

9. Pulmonic Valve Disease

9.1. Stages of Pulmonic Regurgitation

See Table 21 for the stages of severe pulmonic regurgitation (PR).

Table 21. Stages of Severe PR

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
C, D	Severe PR	• Distorted or absent leaflets, annular dilation	• Color jet fills RVOT • CW jet density and contour: dense laminar flow with steep deceleration slope; may terminate abruptly	• Paradoxical septal motion (volume overload pattern) • RV enlargement	• None or variable and dependent on cause of PR and RV function

CW indicates continuous wave; PR, pulmonic regurgitation; RV, right ventricular; and RVOT, right ventricular outflow tract. (515)

Mild-to-moderate PR seen on echocardiography is common and does not require further follow-up or intervention if asymptomatic with normal RV size and function. Significant PR in patients is uncommon. *Primary* PR that follows in the wake of childhood surgery for tetralogy of Fallot or other congenital lesions may progress insidiously and reach severe proportions that threaten RV function without adequate clinical recognition. Its evaluation and management, including indications for valve replacement, are comprehensively reviewed in the "2008 ACC/AHA Guidelines for the Management of Patients With Congenital Heart Disease." The pulmonic valve is rarely involved by IE or rheumatic disease but is susceptible to carcinoid accretion because it also affects the tricuspid valve and results in varying degrees of stenosis and regurgitation. Surgery is considered when symptoms or signs of RV dysfunction have intervened and PR is severe. *Secondary* PR from long-standing pulmonary hypertension and annular dilation is encountered less frequently in the modern era. Treatment should focus on the cause(s) of elevated pulmonary artery pressures.

Supporting Reference: (516)

9.2. Stages of Pulmonic Stenosis

See Table 22 for the stages of severe pulmonic stenosis.

Table 22. Stages of Severe Pulmonic Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
C, D	Severe PS	• Thickened,	• V_{max} >4 m/s; peak	• RVH	• None or

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Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
		distorted, possibly calcified leaflets with systolic doming and/or reduced excursion • Other anatomic abnormalities may be present, such as narrowed RVOT	instantaneous gradient >64 mm Hg	• Possible RV, RA enlargement • Poststenotic enlargement of main PA	variable and dependent on severity of obstruction

PA indicates pulmonary artery; PS, pulmonic stenosis; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; RVOT, right ventricular outflow; and V_{max}, maximal pulmonic valve jet velocity. (8)

Pulmonic stenosis is essentially a congenital disorder. Less common etiologies include carcinoid and obstructing vegetations or tumors. Assessment with TTE alone is usually sufficient for diagnosis and clinical decision making. Indications for percutaneous balloon pulmonic valve commissurotomy and valve replacement are contained in the "2008 ACC/AHA Guidelines for the Management of Patients With Congenital Heart Disease."

Supporting Reference: (516)

American Heart Association.

10. Mixed Valve Disease

10.1. Mixed VHD

10.1.1. Diagnosis and Follow-Up

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For the majority of patients with mixed valve disease, there is usually a predominant valve lesion (i.e., stenosis or regurgitation); further, the symptoms and pathophysiology resemble those of a pure dominant lesion. However, the presence of mixed valve disease poses limitations for noninvasive and invasive techniques used to determine severity. These limitations should be strongly considered in the evaluation of patients with mixed valve disease. For patients with mixed aortic disease and predominant AS, a high gradient and small valve area will be present. Pressure overload results in concentric LV myocardial hypertrophy, usually without chamber enlargement except in late stages of the disease. Symptoms may be present in patients with predominant AS with or without alterations in chamber morphology. Conversely, for patients with mixed aortic disease and predominant AR, the aortic velocity and gradient may be significantly elevated due to regurgitation in the setting of AS, but the aortic valve area is relatively large. Patients with predominant AR will have both pressure and volume overload, resulting in marked increases in LV volume. In these patients, symptoms may be relatively latent due to preload recruitment with compensatory hypertrophy. For patients with mixed mitral disease and predominant MS, a high transmitral gradient and small valve area will be present. Left atrial enlargement occurs with relative preservation of the LV chamber size. Conversely, in patients with mixed mitral disease and predominant MR, LV remodeling will occur in addition to left atrial enlargement. These patients frequently have high transmitral gradients due to the regurgitant flow, but the valve area may be relatively large.

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For patients with mixed valve disease, there is a paucity of data on the natural history of such coexistent conditions. Consequently, the appropriate timing for serial evaluations of these patients is relatively unknown. For patients with predominant lesions (i.e., stenosis or regurgitation), serial evaluations in accordance with recommendations for the predominant valve lesion are generally recommended. Nonetheless, it is important to recognize that the coexistence of stenosis and regurgitation may have pathological consequences that are incremental to the effects of either of these disease states alone. As a result, patients with mixed disease may require serial evaluations at intervals earlier than recommended for single valve lesions.
Supporting References: (517-521)

10.1.2. Medical Therapy

Recommendations for medical therapy follow those for mixed valve disease when there is a predominant valve lesion and other management recommendations for concomitant LV dysfunction. There are no other recommendations for medical therapy specific to patients with mixed valve disease.

10.1.3. Timing of Intervention

For patients with mixed valve disease and a predominant lesion, the need for intervention should generally follow recommendations for a pure dominant lesion. This consideration should be undertaken with attention to symptoms, lesion severity, chamber remodeling, operative risk, and the expected surgical outcome. Timing of intervention must be individualized because coexistence of stenosis and regurgitation may have pathological consequences that are incremental to the effects of either lesion alone. For example, patients with mixed aortic disease will have increased afterload due to both the regurgitant volume and the relatively small aortic valve area. Thus, patients with dominant AR may develop symptoms and require surgery before severe LV enlargement develops. For patients with dominant AS, coexistent regurgitation may be poorly tolerated by a ventricle that is noncompliant due to pressure hypertrophy. An elevated left atrial pressure results from both MS and regurgitation in patients with mixed mitral disease. Thus, patients with mixed mitral disease may develop symptoms or pulmonary hypertension at earlier intervals than has been demonstrated in patients with pure stenosis or regurgitation. The alterations in loading conditions due to mixed valve disease may also lead to cardiac symptoms and chamber remodeling in patients when there is not a predominant lesion (i.e., mixed moderate valve disease). Patients with mixed moderate valve disease present a special management challenge, as there is a paucity of data to guide timing of intervention in these patients.

For those patients with symptoms of uncertain origin, valve intervention may be considered when there are clinical findings or data supportive of significant pathological consequences of the mixed valve lesion. Supportive abnormalities include objective evidence of functional limitation (e.g., severely reduced peak myocardial oxygen consumption attributable to impaired cardiac output) and significantly elevated atrial or ventricular pressures. Exercise hemodynamic studies should be considered for those patients with symptoms that are out of proportion to hemodynamic findings at rest. For example, patients with mixed mitral disease and a relatively low mitral gradient may be particularly susceptible to developing *functional* MS at higher

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transvalvular flow rates due to the concomitant regurgitant volume. In patients with mixed aortic disease, the pathological contribution of aortic regurgitant volume may lessen with exercise due to shortening of diastole. Given the potential limitations of noninvasive assessments, direct pressure measurement with cardiac catheterization may be needed for assessing ventricular filling abnormalities at rest and with exercise in patients with mixed valve disease. Because the indications for intervention have not been well studied in this patient population, the decision to pursue surgical therapy should be individualized, with consideration of patient symptoms, severity of hemodynamic abnormalities, and risk of surgery.

Supporting References: (517-521)

10.1.4. Choice of Intervention

For patients with mixed valve disease, the appropriate interventional therapy is determined by guidelines for the predominant valve lesion with consideration of the severity of the concomitant valve disease. For example, in a patient with predominant AS, TAVR may be considered in patients with moderate but not severe AR, whereas conventional AVR may be a therapeutic option regardless of severity of mixed valve disease. Similarly, percutaneous balloon mitral commissurotomy is a therapeutic option in patients with MS and suitable anatomy if there is mild but not moderate or severe regurgitation. Percutaneous aortic balloon dilation should not be performed if there is moderate or severe regurgitation due to the potential for worsening of the regurgitation with the procedure.

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11. Prosthetic Valves

11.1. Evaluation and Selection of Prosthetic Valves

11.1.1. Diagnosis and Follow-Up: Recommendations

Patients who have undergone valve replacement are not cured but still have serious heart disease. Patients have exchanged native valve disease for prosthetic valve disease and must be followed with the same care as those with native valve disease. The clinical course of patients with prosthetic heart valves is influenced by several factors, including LV dysfunction; progression of other valve disease; pulmonary hypertension; concurrent coronary, myocardial, or aortic disease; and complications of prosthetic heart valves. The interval between routine follow-up visits depends on the patient's valve type, residual heart disease, comorbid conditions, and other clinical factors. Management of anticoagulation should be supervised and monitored frequently by an experienced healthcare professional.

The asymptomatic uncomplicated patient is usually seen at 1-year intervals for a cardiac history and physical examination. ECG and chest x-ray examinations are not routinely indicated but may be appropriate in individual patients. Additional tests that may be considered include hemoglobin and hematocrit in patients receiving chronic anticoagulation. No further echocardiographic testing is required after the initial postoperative evaluation in patients with mechanical valves who are stable and who have no symptoms or clinical evidence of prosthetic valve or ventricular dysfunction or dysfunction of other heart valves.

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Class I

1. **An initial TTE study is recommended in patients after prosthetic valve implantation for evaluation of valve hemodynamics (522-525).** ***(Level of Evidence: B)***

An echocardiographic examination performed 6 weeks to 3 months after valve implantation is an essential component of the first postoperative visit because it allows for an assessment of the effects and results of surgery and serves as a baseline for comparison should complications or deterioration occur later. Doppler TTE provides accurate measurements of transvalvular velocities and pressure gradients as well as detection and quantitation of valvular and paravalvular regurgitation. Normal Doppler transvalvular velocities and gradients vary among different types and sizes of prosthetic valves but are also affected by patient-specific factors, including body size and cardiac output. The postoperative study, recorded when the patient is asymptomatic and in a stable hemodynamic state, provides the normal Doppler flow data for that valve in that patient. In addition to imaging and Doppler flow data for the prosthetic valve, TTE provides assessment of other valve disease(s), pulmonary hypertension, atrial size, LV and RV hypertrophy, LV and RV size and function, and pericardial disease.

Supporting References: (143, 526, 527)

Class I

2. **Repeat TTE is recommended in patients with prosthetic heart valves if there is a change in clinical symptoms or signs suggesting valve dysfunction.** ***(Level of Evidence: C)***

Bioprosthetic valves are prone to tissue degeneration or pannus formation with development of valve regurgitation and/or stenosis. Bioprosthetic valve dysfunction typically presents with the insidious onset of exertional dyspnea or with a louder systolic murmur (MR or AS) or a new diastolic murmur (AR or MS) on physical examination. More abrupt and severe symptoms may occur with bioprosthetic valve endocarditis or with degenerative rupture of a valve cusp.

Patients with mechanical valve dysfunction present with symptoms of HF, systemic thromboembolism, hemolysis, or a new murmur on auscultation. Mechanical valve dysfunction may be due to thrombosis, pannus formation, or IE. Signs or symptoms of mechanical valve dysfunction are often acute or subacute because of more abrupt impairment of leaflet occluder opening or closing by thrombus or pannus. Acute or chronic paravalvular regurgitation may also be seen due to IE or suture dehiscence.

TTE allows evaluation of valve dysfunction based on imaging of leaflet structure and motion, vegetations, and thrombus and Doppler evaluation for prosthetic valve stenosis or regurgitation. Comparison with the baseline postoperative echocardiogram is particularly helpful for detection of prosthetic valve dysfunction.

Supporting References: (528, 529)

Class I

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3. **TEE is recommended when clinical symptoms or signs suggest prosthetic valve dysfunction. *(Level of Evidence: C)***

TTE is the preferred approach for initial assessment of suspected prosthetic valve dysfunction because it allows correct alignment of the Doppler beam with transvalvular flow for measurement of velocity, gradient, and valve area. TTE also allows quantitation of LV volumes and LVEF, an estimate of pulmonary pressures, and evaluation of right heart function. However, the left atrial side of a prosthetic mitral valve is obscured by acoustic shadowing from the TTE approach, resulting in a low sensitivity for detection of prosthetic MR and prosthetic mitral valve thrombus, pannus, or vegetation. TEE provides superior images of the left atrial side of the mitral prosthesis and is accurate for diagnosis of prosthetic mitral valve dysfunction. However, both TTE and TEE are needed for complete evaluation in a patient with suspected prosthetic valve dysfunction, particularly for those with prosthetic aortic valves in whom the posterior aspect of the valve is shadowed on the TTE approach and the anterior aspect of the valve is shadowed on the TEE approach. With suspected mechanical valve stenosis, fluoroscopy or CT imaging of valve occluder motion also is helpful for detection of reduced motion due to pannus or thrombus.

Supporting References: (530, 531)

Class IIa

1. **Annual TTE is reasonable in patients with a bioprosthetic valve after the first 10 years, even in the absence of a change in clinical status. (*Level of Evidence: C)***

The incidence of bioprosthetic valve dysfunction is low within 10 years of valve implantation but increases markedly after that point; as such, routine annual evaluation is a reasonable approach. Earlier evaluation may also be prudent in selected patients at increased risk of early bioprosthetic valve degeneration, including those with renal impairment, diabetes mellitus, abnormal calcium metabolism, systemic inflammatory disease, and in patients <60 years of age. Patients typically remain asymptomatic until valve dysfunction is severe enough to result in adverse hemodynamic consequences, such as LV dilation and systolic dysfunction, pulmonary hypertension, or AF. It may be challenging to distinguish a murmur due to prosthetic MR or AS from the normal postoperative flow murmur, and the diastolic murmurs of prosthetic AR and MS often are very soft and difficult to hear on auscultation. Depending on the valve type and mechanism of regurgitation, some patients with asymptomatic significant prosthetic valve regurgitation may require surgical intervention. For example, if prosthetic regurgitation is due to a bioprosthetic leaflet tear, more severe acute regurgitation may suddenly occur and cause clinical decompensation. Other asymptomatic patients with less severe prosthetic valve regurgitation or with stable valve anatomy can be monitored for evidence of progressive LV dilation and systolic dysfunction with the same criteria for timing of surgical intervention as those for native valve regurgitation. With prosthetic valve stenosis, echocardiographic diagnosis while the patient is asymptomatic alerts the clinician to the need for more frequent follow-up. Patients with asymptomatic prosthetic valve stenosis should be educated about

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symptoms, the likely need for repeat valve intervention, and the importance of promptly reporting new symptoms.

In patients with mechanical valve prostheses, routine annual echocardiographic evaluation is not needed if the postoperative baseline study is normal in the absence of signs or symptoms of valve dysfunction. However, many of these patients require TTE for other indications, such as residual LV systolic dysfunction, pulmonary hypertension, aortic disease, or concurrent valve disease.

Supporting References: (532, 533)

11.1.2. Intervention: Recommendations

See Table 23 for a summary of recommendations for prosthetic valve choice.

Table 23. Summary of Recommendations for Prosthetic Valve Choice

Recommendations	COR	LOE	References
Choice of valve intervention and prosthetic valve type should be a shared decision process	I	C	N/A
A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired	I	C	N/A
A mechanical prosthesis is reasonable for AVR or MVR in patients <60 y of age who do not have a contraindication to anticoagulation	IIa	B	(534-536)
A bioprosthesis is reasonable in patients >70 y of age	IIa	B	(537-540)
Either a bioprosthetic or mechanical valve is reasonable in patients between 60 y and 70 y of age	IIa	B	(541, 542)
Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered in young patients when VKA anticoagulation is contraindicated or undesirable	IIb	C	N/A

AVR indicates aortic valve replacement; COR, Class of Recommendation; LOE, Level of Evidence; MVR, mitral valve replacement; N/A, not applicable; and VKA, vitamin K antagonist.

Circulation
Journal of the American Heart Association

Class I

1. **The choice of valve intervention, that is, repair or replacement, as well as type of prosthetic heart valve, should be a shared decision-making process that accounts for the patient's values and preferences, with full disclosure of the indications for and risks of anticoagulant therapy and the potential need for and risk of reoperation.** ***(Level of Evidence: C)***

The choice of valve prosthesis in an individual patient is based on consideration of several factors, including valve durability, expected hemodynamics for a specific valve type and size, surgical or interventional risk, the potential need for long-term anticoagulation, and patient preferences. Specifically, the tradeoff between risk of reoperation for bioprosthetic valve degeneration and the risk associated with long-term anticoagulation should be discussed in detail with the patient. Surgical or interventional risk for an individual patient is estimated by using the STS PROM score with the online calculator (Section 3.2.4). This information is discussed with the patient and family to allow for shared decision making about the timing and type of intervention. In a patient with a small aortic annulus, patient-prosthesis mismatch of the implanted prosthetic aortic valve may be avoided or reduced by consulting tables of prosthetic valve hemodynamics for the valve types and sizes being

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considered. Aortic annular enlarging procedures may be used when patient-prosthesis mismatch cannot be avoided with any available valve substitute.

Bioprosthetic valves avoid the need for long-term anticoagulation with VKA, such as warfarin, but have limited durability. The risk of need for reoperation with a bioprosthetic valve is inversely related to the patient's age at the time of implantation, with a rate of structural deterioration 15 to 20 years after implantation of only 10% in patients 70 years of age at the time of implantation compared with 90% in those 20 years of age at the time of implantation. Mechanical valves are durable in patients of any age with a low risk of reoperation, and current VKA therapeutic management strategies are associated with a low risk of thromboembolism and bleeding. Some patients prefer to avoid repeat surgery and are willing to accept the risks and inconvenience of lifelong anticoagulant therapy. A mechanical valve might be prudent for patients in whom a second surgical procedure would be high risk; for example, those with prior radiation therapy or a porcelain aorta. Other patients are unwilling to consider long-term VKA therapy due to the inconvenience of monitoring, the attendant dietary and medication interactions, and the need to restrict participation in some types of athletic activity. In women who desire subsequent pregnancy, the issue of anticoagulation during pregnancy is a consideration (Section 13).

In patients who are being treated with long-term VKA anticoagulation before valve surgery, a mechanical valve may be appropriate, given its greater durability compared with a bioprosthetic valve and the need for continued VKA anticoagulation even if a bioprosthetic valve is implanted. However, if interruption of VKA therapy is necessary for noncardiac procedures, bridging therapy with other anticoagulants may be needed if a mechanical valve is present, whereas stopping and restarting VKA therapy for other indications may be simpler. Specific clinical circumstances, comorbid conditions, and patient preferences should be considered when deciding between a bioprosthetic and mechanical valve in patients receiving VKA therapy for indications other than the prosthetic valve itself.

Supporting References: (532, 533, 543-545)

Class I

2. **A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. *(Level of Evidence: C)***

Anticoagulant therapy with VKA is necessary in all patients with a mechanical valve to prevent valve thrombosis and thromboembolic events. If anticoagulation is contraindicated or if the patient refuses VKA therapy, an alternate valve choice is appropriate.

Class IIa

1. **A mechanical prosthesis is reasonable for AVR or MVR in patients less than 60 years of age who do not have a contraindication to anticoagulation (534-536). *(Level of Evidence: B)***

In a prospective randomized study of 575 patients undergoing older-generation mechanical versus bioprosthetic valve replacement, overall survival was similar at 15 years in both groups. However, in patients <65 years of age undergoing AVR, primary valve failure occurred in 26% of those with a bioprosthetic valve compared with

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0% of patients with a mechanical valve. Similarly, in those <65 years of age undergoing MVR, primary valve failure occurred in 44% of patients with a bioprosthetic mitral valve compared with 4% with a mechanical mitral valve (p=0.0001). In a propensity score–matched comparison of 103 patients <60 years of age undergoing mechanical versus biological AVR, those with a mechanical valve had lower mortality rates (HR: 0.243; 95% CI: 0.054 to 0.923; p=0.038) despite similar rates of valve-related complications. This is possibly related to better valve hemodynamics and the beneficial effects of anticoagulant therapy in those with a mechanical valve.

Overall, patients <60 years of age at the time of valve implantation have a higher incidence of primary structural deterioration and a reoperation rate as high as 40% for patients 50 years of age, 55% for patients 40 years of age, 75% for patients 30 years of age, and 90% for patients 20 years of age. Anticoagulation with VKA has an acceptable risk of complications in patients <60 years of age, particularly in compliant patients with appropriate monitoring of INR levels. Thus, the balance between valve durability versus risk of bleeding and thromboembolic events favors the choice of a mechanical valve in patients <60 years of age.

Supporting References: (533, 536, 546)

Class IIa

2. **A bioprosthesis is reasonable in patients more than 70 years of age (537-540). *(Level of Evidence: B)***

In patients >70 years of age at the time of bioprosthetic valve implantation, the likelihood of primary structural deterioration at 15 to 20 years is only about 10%. In addition, older patients are at higher risk of bleeding complications related to VKA therapy and more often require interruption of VKA therapy for noncardiac surgical and interventional procedures. In the United States, the expected remaining years of life at 70 years of age is 13.6 years for a man and 15.9 years for a woman; at 80 years of age the expected remaining years of life is 7.8 years for men and 9.3 years for women. Thus, it is reasonable to use a bioprosthetic valve in patients >70 years of age to avoid the risks of anticoagulation because the durability of the valve exceeds the expected years of life. Data from 41,227 patients in the Society for Cardiothoracic Surgery in the Great Britain and Ireland National database between 2004 and 2009 show that the proportion of patients >70 years of age who receive a biological prosthesis at the time of valve replacement has increased from 87% to 96%, with no evidence for an increase in adverse events.

Supporting References: (41, 533, 546)

Class IIa

3. **Either a bioprosthetic or mechanical valve is reasonable in patients between 60 and 70 years of age (541, 542). *(Level of Evidence: B)***

Outcomes are similar with implantation of either a bioprosthetic or mechanical valve for patients between 60 and 70 years of age at the time of surgery. In the Edinburgh Heart Valve Study of 533 patients (mean age 54.4±10.4 years) undergoing valve surgery, there was no difference in long-term survival between those

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randomized to a Bjork-Shiley mechanical prosthesis or a porcine prosthesis (log-rank test: p=0.39). In a prospective randomized Italian study of 310 patients between 55 and 70 years of age, there was no difference in overall survival at 13 years between those receiving a mechanical valve compared with those who received a bioprosthetic valve. The linearized rates of thromboembolism, bleeding, IE, and major adverse prosthesis-related events were no different between the 2 valve types, but valve failures and reoperations were more frequent in the bioprosthetic valve group compared with the mechanical valve group (p=0.0001 and p=0.0003, respectively).

Although the evidence supports the use of either a mechanical or bioprosthetic valve in patients 60 to 70 years of age, patient preferences should also be considered. According to data on 41,227 patients in the Society for Cardiothoracic Surgery in the Great Britain and Ireland National database collected between 2004 and 2009, the proportion of patients 60 to 65 years of age who received a bioprosthesis at the time of valve replacement increased from 37% to 55%; in those 65 to 70 years of age, the proportion increased from 62% to 78%.
Supporting References: (532, 533, 543, 546)

Class IIb

1. **Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered in young patients when VKA anticoagulation is contraindicated or undesirable.** ***(Level of Evidence: C)***

Replacement of the aortic valve with a pulmonary autograft (the Ross procedure) is a complex operation intended to provide an autologous substitute for the patient's diseased aortic valve by relocating the pulmonic valve into the aortic position and subsequently replacing the pulmonic valve with a homograft. It is a surgical challenge and requires an experienced surgical team with exceptional surgical expertise. In the most experienced hands, hospital mortality can be similar to mortality for a simple bioprosthetic or mechanical valve replacement. Expansion of the Ross procedure to a broader group of surgeons with less focused experience has been difficult. The failure mode of the Ross procedure is most often due to regurgitation of the pulmonary autograft (the neoaortic valve) in the second decade after the operation. Regurgitation typically is due to leaflet prolapse if the autograft is implanted in the subcoronary position or to aortic sinus dilation if the autograft is implanted starting at the aortic sinuses. Surgical reinforcement techniques have been used to prevent dilation of the neoaortic sinuses. Some surgeons have advocated placing the pulmonic valve within a Dacron conduit. Still others have returned to placing the neoaortic valve in a subcoronary position with a reinforced native aorta. The outcome of these new procedures, with data extending into the second decade after operation, is not yet available.

In a small (n=228) RCT comparing pulmonary autografts with aortic valve allografts, the HR for death at 10 years was 4.61 (p=0.006) in those receiving an allograft compared with those with a pulmonary autograft AVR, with survival in the autograft group similar to an age-matched general population. Freedom from reoperation for the aortic sinuses and ascending aorta was 99% in the autograft group and 82% in the allograft group. Freedom from severe regurgitation of the neoaortic valve was 94% at 10 years. However, these

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outstanding results have not been generally replicated. In addition, an allograft valve is not the ideal comparator, given current outcomes with bioprosthetic valves.

In addition to reoperation for neoaortic valve regurgitation, at least half of the new pulmonic homograft valve implants will require intervention during the second decade. This is obviously a concern for young patients who began with single valve disease and then face a lifetime of dealing with both pulmonic homograft and neoaortic valve disease. Calcification of the homograft and adhesions between the homograft and neoaorta may increase the difficulty of reoperation.

The Ross procedure is an effective procedure in the hands of a small group of focused and experienced surgeons. It is a risky procedure in the hands of surgeons who perform it only occasionally. The procedure should be reserved for patients in whom anticoagulation is either contraindicated or very undesirable, and it should be performed only by surgeons experienced in complex surgery involving the aortic valve, sinuses, and ascending aorta.

Supporting References: (547-549)

See Online Data Supplement 20 for more information on choice of valve prosthesis (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

11.2. Antithrombotic Therapy for Prosthetic Valves

11.2.1. Diagnosis and Follow-Up

Effective antithrombotic therapy in patients with mechanical heart valves requires continuous effective VKA anticoagulation with an INR in the target range. It is preferable to specify a single INR target in each patient, recognizing that the acceptable range is 0.5 INR units on each side of this target; this is preferable because it avoids patients having INR values consistently near the upper or lower edge of the range. In addition, fluctuations in INR are associated with increased incidence of complications in patients with prosthetic valves, so patients and caregivers should strive to attain the single INR value. The effects of VKA anticoagulation vary with the specific medication, absorption of medication, effects of various foods and medications, and changes in liver function. Most of the published studies on VKA therapy used warfarin, although other coumarin agents are used on a worldwide basis. In clinical practice, a program of patient education and close surveillance by an experienced healthcare professional with periodic monitoring of the INR is necessary. Patient monitoring by hospital-based anticoagulation clinics results in lower complication rates compared with standard care and is cost-effective due to lower rates of bleeding and hemorrhagic complications. Periodic direct patient contact and telephone encounters with the anticoagulation clinic pharmacists are equally effective in reducing complication rates. Self-monitoring with home INR measurement devices is another option for educated and motivated patients.

Supporting References: (550-555)

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11.2.2. Medical Therapy: Recommendations

Class I

1. **Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve (556-558).** ***(Level of Evidence: A)***

All patients with mechanical valves require anticoagulant therapy. In addition to the thrombogenicity of the intravascular prosthetic material, mechanical valves impose abnormal flow conditions, with zones of low flow within their components, as well as areas of high-shear stress, which can cause platelet activation, leading to valve thrombosis and embolic events. Life-long therapy with an oral VKA at an INR goal appropriate for the comorbidity of the patient and the type and position of the mechanical valve prosthesis is recommended to decrease the incidence of thromboembolism and the associated morbidity (e.g., ischemic stroke, cerebrovascular accident, and peripheral systemic embolism). Cumulative data show that anticoagulation with a VKA is protective against valve thrombosis (OR: 0.11; 95% CI: 0.07 to 0.2) and thromboembolic events (OR: 0.21; 95% CI: 0.16 to 0.27).

Many centers initiate heparin early after surgery for anticoagulation until the INR reaches the therapeutic range. Bridging anticoagulation is typically started once postoperative bleeding is no longer an issue. Some centers use subcutaneous low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), whereas other centers continue to prefer intravenous UFH.

Supporting References: (12, 556, 559, 560)

Class I

2. **Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical AVR (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism (561-563).** ***(Level of Evidence: B)***

The intensity of anticoagulation in a patient with a mechanical aortic valve prosthesis should be optimized so that protection from thromboembolism and valve thrombosis is achieved without excess risk of bleeding. The rate of thromboembolism in patients with bileaflet mechanical AVR on VKA and antiplatelet regimen is estimated to be 0.53% per patient-year over the INR range of 2.0 to 4.5. In a large retrospective study, adverse events increased if the INR was >4.0 in patients with mechanical AVR. In patients with the new-generation AVR without other risk factors for thromboembolism, the risk of thromboembolic events was similar, but the risk of hemorrhage was lower in the group with an INR of 2.0 to 3.0 versus the group with an INR of 3.0 to 4.5 ($p<0.01$). In a study comparing an INR target of 1.5 to 2.5 with the conventional 2.0 to 3.0 in 396 patients with low-risk mechanical aortic prosthetic valves and no other risk factors, the lower INR target was noninferior, but the quality of the evidence was low. Thus, for bileaflet and current-generation single tilting disc valve prostheses in the aortic position, an INR of 2.5 (between 2.0 and 3.0) provides a reasonable balance between optimal anticoagulation and a low risk of bleeding for mechanical aortic valves with a low thromboembolic risk.

Supporting Reference: (12)

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Class I

3. **Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage) (564).** ***(Level of Evidence: B)***

In patients with an aortic mechanical prosthesis who are at higher risk of thromboembolic complications, INR should be maintained at 3.0 (range 2.5 to 3.5). These patients include those with AF, previous thromboembolism, and a hypercoagulable state. Many would also include patients with severe LV dysfunction in this higher-risk group.

Supporting Reference: (12)

Class I

4. **Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR (564, 565).** ***(Level of Evidence: B)***

In patients with mechanical prostheses, the incidence of thromboembolism is higher for the mitral than the aortic position, and the rate of thromboembolism is lower in patients with a higher INR goal compared with those with a lower target INR. In the GELIA (German Experience with Low Intensity Anticoagulation) study of patients with a mechanical mitral prosthesis, a lower INR (2.0 to 3.5) was associated with lower survival rates than a higher target INR range (2.5 to 4.5) in those with a second mechanical valve. Patient compliance may be challenging with higher INR goals. In 1 study, patients with a target INR between 2.0 and 3.5 were within that range 74.5% of the time. In contrast, patients with a target INR of 3.0 to 4.5 were within range only 44.5% of the time. An INR target of 3.0 (range 2.5 to 3.5) provides a reasonable balance between the risks of under- or overanticoagulation in patients with a mechanical mitral valve.

Supporting References: (12, 562)

Class I

5. **Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (566, 567).** ***(Level of Evidence: A)***

Aspirin is recommended for all patients with prosthetic heart valves, including those with mechanical prosthetic valves receiving VKA therapy. Even with the use of VKA, the risk of thromboemboli is 1% to 2% per year.

The addition of aspirin 100 mg daily to oral VKA anticoagulation decreases the incidence of major embolism or death (1.9% versus 8.5% per year; $p<0.001$), with the stroke rate decreasing to 1.3% per year versus 4.2% per year ($p<0.027$) and overall mortality to 2.8% per year versus 7.4% per year ($p<0.01$). The addition of low-dose aspirin (75 mg to 100 mg per day) to VKA therapy (INR 2.0 to 3.5) also decreases mortality due to other cardiovascular diseases. The combination of low-dose aspirin and VKA is associated with a slightly increased risk of minor bleeding such as epistaxis, bruising, and hematuria, but the risk of major

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bleeding does not differ significantly between those who received aspirin (8.5%) versus those who did not (6.6%; p=0.43). The risk of GI irritation and hemorrhage with aspirin is dose dependent over the range of 100 mg to 1,000 mg per day, but the antiplatelet effects are independent of dose over this range. The addition of aspirin (75 mg to 100 mg per day) to VKA should be strongly considered unless there is a contraindication to the use of aspirin (i.e., bleeding or aspirin intolerance). This combination is particularly appropriate in patients who have had an embolus while on VKA therapy with a therapeutic INR, those with known vascular disease, and those who are known to be particularly hypercoagulable.

Supporting References: (12, 568-571)

Class IIa

1. **Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve (572-575). (*Level of Evidence: B)***

The risk of a clinical thromboembolism is on average 0.7% per year in patients with biological valves in sinus rhythm; this figure is derived from several studies in which the majority of patients were not undergoing therapy with VKA. Among patients with bioprosthetic valves, those with mitral prostheses have a higher rate of thromboembolism than those with aortic prostheses in the long term (2.4% per patient-year versus 1.9% per patient-year, respectively). In a prospective study of bioprosthetic valves in patients with AVR who were in sinus rhythm and had no other indications for anticoagulation, the incidence of thromboembolic events, bleeding, and death was similar between those who received aspirin or aspirin-like antiplatelet agents only versus those who received VKA. There are no studies examining the long-term effect of antiplatelet agents in patients with bioprosthetic MVR or mitral valve repair, but the beneficial effects seen with bioprosthetic aortic valves are presumed to apply to mitral valves as well.

Supporting Reference: (12)

Class IIa

2. **Anticoagulation with a VKA is reasonable for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5 (576). *(Level of Evidence: C)***

The risk of ischemic stroke after all types of mitral valve surgery is about 2% at 30 days, 3% at 180 days, and 8% at 5 years. This is observed even with routine use of early heparin followed by VKA in patients with a mechanical valve or other indications for long-term anticoagulant therapy. The risk of ischemic stroke at 5 years is lower with mitral valve repair (6.1%±0.9%) compared with bioprosthetic (8.0%±2.1%) and mechanical valve replacement (16.1%±2.7%). In 1 study, patients with a bioprosthetic MVR who received anticoagulation had a lower rate of thromboembolism than those who did not receive therapy with VKA (2.5% per year with anticoagulation versus 3.9% per year without anticoagulation; p=0.05). However, another study showed that even with routine anticoagulation early after valve surgery, the incidence of ischemic stroke within the first 30 postoperative days was higher after replacement with a biological prosthesis (4.6%±1.5%; p<0.0001) than after mitral valve repair (1.5%±0.4%) or replacement with a mechanical prosthesis (1.3%±0.8%; p<0.001). Thus,

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anticoagulation with a target INR of 2.5 (range 2.0 to 3.0) is reasonable early after bioprosthetic mitral valve implantation.

Many centers start heparin as soon as the risk of surgical bleeding is acceptable (usually within 24 to 48 hours), with maintenance of a therapeutic partial thromboplastin time. After an overlap of heparin and VKA for 3 to 5 days, heparin may be discontinued when the INR reaches 2.5. After 3 months, the tissue valve can be treated like native valve disease, and VKA can be discontinued in more than two thirds of patients with biological valves. In the remaining patients with associated risk factors for thromboembolism, such as AF, previous thromboembolism, or hypercoagulable condition, lifelong VKA therapy is indicated to achieve an INR of 2 to 3.

Supporting References: (572-574, 577-582)

Class IIb

1. **Anticoagulation, with a VKA, to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic AVR (583). *(Level of Evidence: B)***

Patients with a bioprosthetic aortic valve are at a higher risk of ischemic stroke or peripheral embolism than the normal population, particularly in the first 90 days after valve replacement. Anticoagulation early after valve implantation is intended to decrease the risk of thromboembolism until the prosthetic valve is fully endothelialized. The potential benefit of anticoagulation therapy must be weighed against the risk for bleeding, particularly in patients who are at low risk for thromboembolism (e.g., those in sinus rhythm with normal LV function, no history of thromboembolism, or history of hypercoagulable conditions). Small RCTs have not established benefit for anticoagulation after implantation of a bioprosthetic AVR; however, a large observational registry demonstrated benefit without a significantly increased bleeding risk. In 4,075 patients undergoing isolated bioprosthetic AVR with a median duration of follow-up of 6.57 person-years, the estimated rate of strokes per 100 person-years was 7.00 (95% CI: 4.07 to 12.06) in patients not treated with VKA versus 2.69 (95% CI: 1.49 to 4.87) in those treated with VKA (HR: 2.46; 95% CI: 1.09 to 5.55). The lower event rates in those on VKA persisted at 6 months, with a cardiovascular death rate of 6.50 per 100 person-years (95% CI: 4.67 to 9.06) in those not on VKA therapy compared with 2.08 (95% CI: 0.99 to 4.36) in those on VKA therapy (adjusted internal rate of return: 3.51; 95% CI: 1.54 to 8.03) for events within 90 to 179 days after surgery. Thus, anticoagulation with an INR target of 2.5 (range 2.0 to 3.0) may be reasonable for at least 3 months, and perhaps as long as 6 months, after bioprosthetic AVR.

Supporting References: (572, 574, 583-586)

Class IIb

2. **Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily. (*Level of Evidence: C)***

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During TAVR, a biological prosthesis mounted on a metallic expandable frame is inserted transcutaneously within the native aortic valve with stenosis. In prospective RCTs of balloon-expandable TAVR for treatment of AS, the research protocol included dual antiplatelet therapy with aspirin and clopidogrel for the first 6 months to minimize the risk of thromboembolism. The current recommendation is based on outcomes in these published studies, although the issue of antiplatelet therapy was not assessed. A small prospective, RCT, single-center study of 79 patients receiving self-expanding TAVR did not show a difference in the composite of major adverse cardiac and cerebrovascular events, defined as death from any cause, MI, major stroke, urgent or emergency conversion to surgery, or life-threatening bleeding between aspirin and clopidogrel versus aspirin alone at both 30 days (13% versus 15%; p=0.71) and 6 months (18% versus 15%; p=0.85).
Supporting References: (79, 171, 587, 588)

Class III: Harm

1. **Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses (589-591).** ***(Level of Evidence: B)***

The U.S. Food and Drug Administration has approved new anticoagulants that are direct thrombin inhibitors or factor Xa inhibitors (dabigatran, apixaban, and rivaroxaban) for anticoagulant prophylaxis in patients with AF not caused by VHD. Several case reports have demonstrated thrombosis on mechanical heart valves despite therapeutic dosing with dabigatran. The RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial was stopped prematurely for excessive thrombotic complications in the dabigatran arm. After enrollment of 252 patients, ischemic or unspecified stroke occurred in 9 patients (5%) randomized to dabigatran compared with no patients treated with warfarin. In the dabigatran group, 15 patients (9%) reached the composite endpoint of stroke, transient ischemic attack, systemic embolism, MI, or death compared with 4 patients (5%) in the warfarin group (HR in the dabigatran group: 1.94; 95% CI: 0.64 to 5.86; p=0.24). In addition, a major bleeding episode occurred in 7 patients (4%) in the dabigatran group and 2 patients (2%) in the warfarin group, and bleeding of any type occurred in 45 patients (27%) and 10 patients (12%), respectively (HR: 2.45; 95% CI: 1.23 to 4.86; p=0.01). The Food and Drug Administration has issued a specific contraindication for use of this product in patients with mechanical heart valves. These agents are also not recommended, due to lack of data on their safety and effectiveness, in patients with bioprosthetic valves who require anticoagulation.
Supporting References: (591-594)

11.3. Bridging Therapy for Prosthetic Valves

11.3.1. Diagnosis and Follow-Up

The management of patients with mechanical heart valves in whom interruption of anticoagulation therapy is needed for diagnostic or surgical procedures should take into account the type of procedure, risk factors, and type, location, and number of heart valve prosthesis(es).

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11.3.2. Medical Therapy: Recommendations

Class I

1. **Continuation of VKA anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled. *(Level of Evidence: C)***

Management of antithrombotic therapy must be individualized, but some generalizations apply. Antithrombotic therapy should not be stopped for procedures in which bleeding is unlikely or would be inconsequential if it occurred (i.e., surgery on the skin, dental cleaning, or simple treatment for dental caries). Eye surgery, particularly for cataracts or glaucoma, is usually associated with very little bleeding and thus is frequently performed without alterations to antithrombotic treatment.

Class I

2. **Temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures. *(Level of Evidence: C)***

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. In patients with a bileaflet mechanical aortic valve and no other risk factors for thromboembolism, the risk of stopping VKA is relatively slight if the drug is withheld for only a few days. In these low-risk patients, the inconvenience and expense of bridging anticoagulation can be avoided. When it is necessary to interrupt VKA therapy, VKA is stopped 2 to 4 days before the procedure (so the INR falls to <1.5 for major surgical procedures) and restarted as soon as bleeding risk allows, typically 12 to 24 hours after surgery.

Supporting References: (595, 596)

Class I

3. **Bridging anticoagulation with either intravenous UFH or subcutaneous LMWH is recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR. *(Level of Evidence: C)***

In patients at higher risk of thromboembolism during interruption of VKA anticoagulation, the risk of an adverse event can be minimized by anticoagulation with alternative agents that can be stopped right before and restarted right after the surgical procedure (e.g., "bridging therapy"). Patients at high risk of thrombosis include all patients with mechanical MVR or tricuspid valve replacements and patients with an AVR and any risk factors for thromboembolism. Such risk factors include AF, previous thromboembolism, hypercoagulable condition, older-generation mechanical valves, LV systolic dysfunction (LVEF <30%), or >1 mechanical valve.

When interruption of VKA therapy is needed, VKA is stopped 2 to 4 days before the procedure (so the INR falls to <1.5 for major surgical procedures) and restarted as soon as bleeding risk allows, typically 12 to 24 hours after surgery. Bridging anticoagulation with intravenous UFH or subcutaneous LMWH is started when

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INR is <2.0 (usually about 48 hours before surgery) and stopped 4 to 6 hours (for intravenous UFH) or 12 hours (for subcutaneous LMWH) before the procedure. When LMWH is used, therapeutic weight-adjusted doses are given twice daily. One study of bridging therapy for interruption of VKA included 215 patients with mechanical valves. In the total group of 650 patients, the risk of thromboembolism (including possible events) was 0.62%, with 95% CI: 0.17% to 1.57%. Major bleeding occurred in 0.95% (0.34% to 2.00%). Most studies using LMWH used enoxaparin for therapy. The use of bridging heparin after surgery must be individualized, depending on risk of bleeding and risk of thrombosis.

The acceptable level of anticoagulation in patients undergoing cardiac catheterization depends on the specific procedure being performed. For procedures with a low bleeding risk, such as coronary angiography from the radial approach, only slight modification in VKA dosing is needed. With interventional procedures at higher risk, many clinicians prefer to stop VKA anticoagulation and use bridging therapy as is done for other surgical procedures.

Supporting References: (597-599)

Class IIa

1. **Administration of fresh frozen plasma or prothrombin complex concentrate is reasonable in patients with mechanical valves receiving VKA therapy who require emergency noncardiac surgery or invasive procedures.** ***(Level of Evidence: C)***

Because VKA inhibits production of several proteins involved in the coagulation cascade, the anticoagulant effect persists until adequate levels of these proteins are achieved after stopping warfarin therapy, a process that takes at least 48 to 72 hours. In patients with mechanical valves on long-term warfarin therapy who require emergency surgery or invasive procedures, anticoagulation can be reversed by administration of fresh frozen plasma or intravenous prothrombin complex concentrate. Administration of low-dose (1 mg to 2 mg) oral vitamin K may be added because the effect of fresh frozen plasma or prothrombin complex has a shorter half-life than the effects of VKA therapy. Higher doses of vitamin K are discouraged to avoid difficulty in achieving a therapeutic INR after the procedure.

Supporting References: (600-602)

See Online Data Supplement 21 for more information on bridging therapy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

11.4. Excessive Anticoagulation and Serious Bleeding With Prosthetic Valves: Recommendation

See Figure 6 for anticoagulation for prosthetic valves.

Class IIa

1. **Administration of fresh frozen plasma or prothrombin complex concentrate is reasonable in patients with mechanical valves and uncontrollable bleeding who require reversal of anticoagulation (601, 602).** ***(Level of Evidence: B)***

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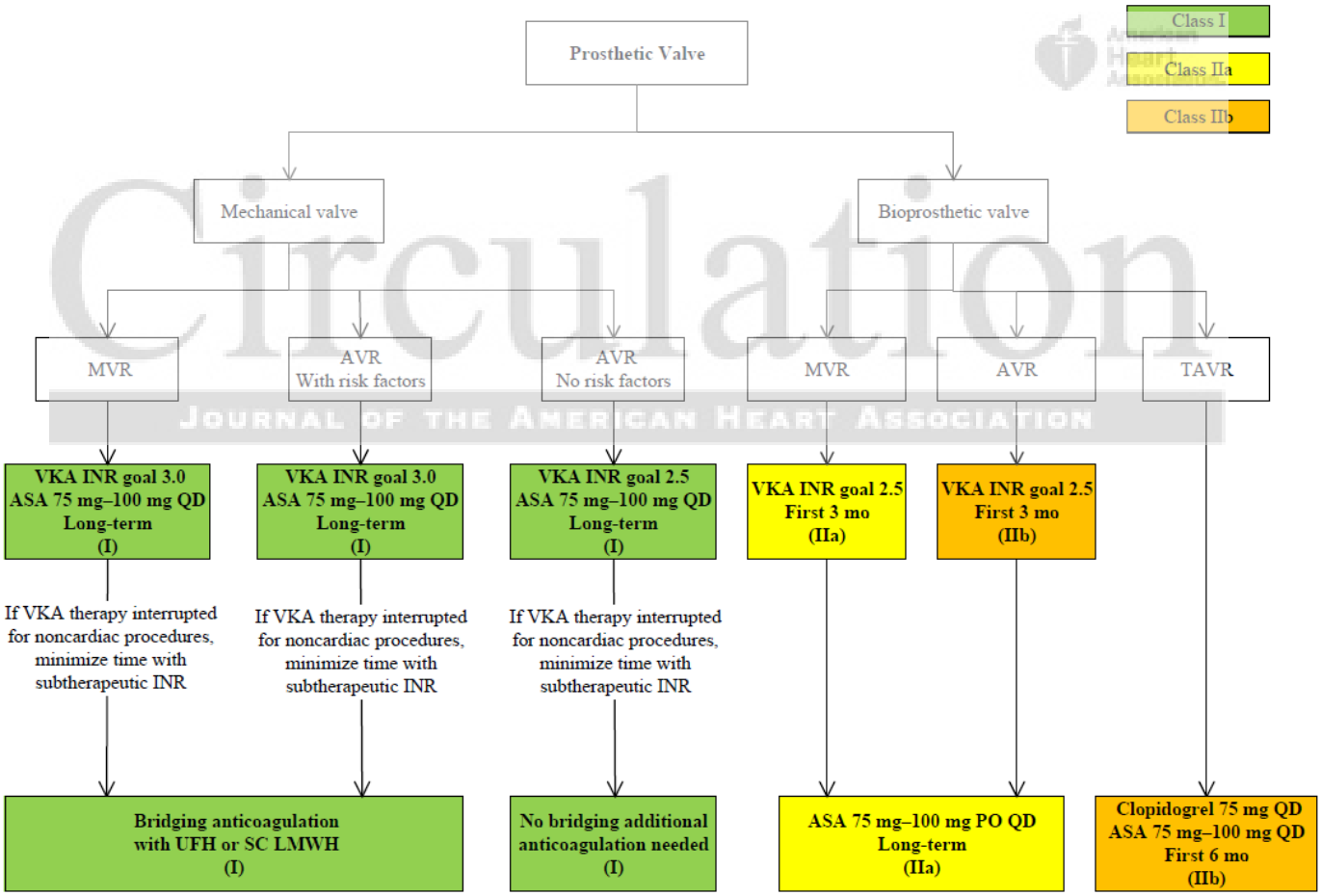
Excessive anticoagulation (INR ≥5) greatly increases the risk of hemorrhage. However, a rapid decrease in the INR that leads to INR falling below the therapeutic level increases the risk of thromboembolism. High-dose vitamin K should not be given routinely, because this may create a hypercoagulable condition. In most patients with an INR of 5 to 10, excessive anticoagulation can be managed by withholding VKA and monitoring the level of anticoagulation with serial INR determinations. In patients with an INR >10 who are not bleeding, it is prudent to administer 1 mg to 2.5 mg of oral vitamin K1 (phytonadione) in addition to holding VKA therapy. When the INR falls to a safe level, VKA therapy is restarted with the dose adjusted as needed to maintain therapeutic anticoagulation. In emergency situations, such as uncontrollable bleeding, administration of fresh frozen plasma or prothrombin complex concentrate is reasonable because the onset of action of vitamin K is very slow.

Supporting References: (600, 603)

Figure 6. Anticoagulation for Prosthetic Valves



Risk factors include AF, previous thromboembolism, LV dysfunction, hypercoagulable condition, and older-generation mechanical AVR.

AF indicates atrial fibrillation; ASA, aspirin; AVR, aortic valve replacement; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; PO, by mouth; QD, every day; SC, subcutaneous; TAVR, transcatheter aortic valve replacement; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

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11.5. Thromboembolic Events With Prosthetic Valves

11.5.1. Diagnosis and Follow-Up

The annual risk of thromboembolic events in patients with a mechanical heart valve is 1% to 2% versus 0.7% with a bioprosthetic valve, even with appropriate antithrombotic therapy. Many complications are likely to be related to suboptimal anticoagulation; even in clinical trials, the time in therapeutic range for patients on VKA varies from only 60% to 70%. However, embolic events do occur even in patients who are in the therapeutic range at every testing interval. Annual follow-up in patients with prosthetic heart valves should include review of the adequacy of anticoagulation and any issues related to compliance with medical therapy. Screening questions for symptoms that may be related to embolic events are especially important if anticoagulation has been suboptimal. Patients should be educated about symptoms related to embolic events and instructed to promptly report to a healthcare provider should symptoms occur. TTE is the first step in evaluation of suspected prosthetic valve thromboembolism to evaluate valve hemodynamics in comparison to previous studies, and TEE often is needed, particularly for mitral prosthetic valves. However, the prosthetic valve should be considered the source of thromboembolism even if echocardiographic findings are unchanged.

11.5.2. Medical Therapy

In patients on VKA anticoagulation and aspirin 75 mg to 100 mg daily for a mechanical valve who have a definite embolic episode, it is important to document the adequacy of the anticoagulation, including the time within therapeutic range. If there have been periods in which the INR has been documented to be subtherapeutic, appropriate steps to ensure adequate anticoagulation should be taken. If embolic events have occurred despite a therapeutic INR when other contraindications are not present, a prudent approach to antithrombotic therapy is:

- Increase the INR goal from 2.5 (range 2.0 to 3.0) to an INR goal of 3.0 (range 2.5 to 3.5) for patients with an AVR; or, increase the INR goal from 3.0 (range 2.5 to 3.5) to an INR goal of 4.0 (range 3.5 to 4.5) for patients with an MVR.

In patients with a bioprosthetic valve with embolic events who are only on aspirin 75 mg to 100 mg daily, a possible approach includes consideration of anticoagulation with a VKA.

11.5.3. Intervention

Embolic events in patients with prosthetic heart valves should be managed by ensuring optimal anticoagulation and antiplatelet therapy. Measures to improve patient compliance, including patient education and more frequent monitoring, should be instituted. Studies show that patients on anticoagulation with VKA who are managed by a dedicated pharmacist-led anticoagulation clinic have lower rates of bleeding and thromboembolism compared with conventional monitoring by a clinician's office. Surgical intervention is rarely needed for recurrent thromboembolic events but might be considered in some situations. In patients with degenerated bioprosthetic valves, calcific emboli may complicate thrombotic embolism, often in association with prosthetic valve stenosis

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and/or regurgitation. In patients with mechanical valves who have recurrent serious adverse effects of over- or underanticoagulation despite all efforts to improve compliance, replacement of the mechanical valve with a bioprosthetic valve might be considered after a discussion of the potential risks and benefits of this approach.

11.6. Prosthetic Valve Thrombosis

See Figure 7 for evaluation and management of suspected valve thrombosis.

11.6.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **TTE is indicated in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity and follow resolution of valve dysfunction (604, 605).** ***(Level of Evidence: B)***

Obstruction of prosthetic heart valves may be caused by thrombus formation, pannus ingrowth, or a combination of both. Mechanical prosthetic heart valve thrombosis has a prevalence of only 0.3% to 1.3% per patient-year in developed countries but is as high as 6.1% per patient-year in developing countries. Bioprosthetic valve thrombosis is less common. Differentiation of valve dysfunction due to thrombus versus fibrous tissue ingrowth (pannus) is challenging because the clinical presentations are similar. Thrombus is more likely when there is a history of inadequate anticoagulation and with more acute onset of valve dysfunction and symptoms. Although fluoroscopy or CT imaging can be used to evaluate the leaflet motion of an obstructed mechanical prosthesis, the etiology and hemodynamic impact are best evaluated by echocardiography. TTE allows evaluation of valve hemodynamics and detection of valve stenosis or regurgitation. Leaflet motion and thrombus may be visualized in some patients, but TEE is more sensitive for detection of valve thrombosis, especially of the mitral valve. Transthoracic imaging also allows measurement of LV size and systolic function, left atrial size, right heart function, and an estimation of pulmonary pressures.

Clinical evaluation, including auscultation of diminished or abolished clicks together with new systolic or diastolic murmurs, is the first step in the routine assessment of patients with a prosthetic heart valve but is unreliable for detection of valve thrombosis. TTE allows detection of prosthetic valve dysfunction and quantitation of stenosis and regurgitation but is inadequate for evaluation of the presence and size of thrombus or valve occluder motion.

Class I

2. **TEE is indicated in patients with suspected prosthetic valve thrombosis to assess thrombus size and valve motion (605-607).** ***(Level of Evidence: B)***

TEE allows direct imaging of mechanical valve thrombosis, particularly for thrombi on the left atrial side of the mitral valve, which is obscured by shadowing on TTE imaging. Compared with chronic fibrous ingrowth or pannus, thrombi tend to be larger, less dense, and more mobile than pannus on ultrasound imaging. Thrombus size, measured on TEE, is a significant independent predictor of outcome after thrombolysis of an obstructed prosthetic heart valve. Multivariate analysis of 107 patients with thrombosed heart valve prostheses revealed

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that prior history of stroke (OR: 4.55; 95% CI: 1.35 to 15.38) and thrombus area by TEE (OR: 2.41 per 1.0 cm^2; CI: 1.12 to 5.19) were independent predictors of complications after thrombolysis. A thrombus area <0.8 cm^2 identified patients at lower risk for complications from thrombolysis, irrespective of NYHA classification. TEE should be used to identify lower-risk patients for thrombolysis.

Supporting References: (605-607)

Class IIa

1. **Fluoroscopy or CT is reasonable in patients with suspected valve thrombosis to assess valve motion. *(Level of Evidence: C)***

Fluoroscopy and CT are alternative imaging techniques for evaluation of mechanical valve "leaflet" motion, particularly in patients with prosthetic aortic valves, which are difficult to image by either TTE or TEE. CT is best suited for measurement of valve opening angles because 3D image acquisition allows postacquisition analysis from multiple views. CT imaging may also allow visualization of pannus or thrombus in patients with mechanical or bioprosthetic valves.

11.6.2. Medical Therapy: Recommendations

Class IIa

1. **Fibrinolytic therapy is reasonable for patients with a thrombosed left-sided prosthetic heart valve, recent onset (<14 days) of NYHA class I to II symptoms, and a small thrombus (<0.8 cm^2) (605, 608). *(Level of Evidence: B)***

Although fibrinolytic therapy of a left-sided obstructed prosthetic heart valve is associated with an overall rate of thromboembolism and bleeding of 17.8%, the degree of risk is directly related to thrombus size. When thrombus area is measured in the 2D TEE view showing the largest thrombus size, an area of 0.8 cm^2 provides a useful breakpoint for clinical decision making. A mobile thrombus or a length >5 mm to 10 mm is also associated with increased embolic risk. Patients with a small thrombus (<1.0 cm in diameter or 0.8 cm^2 in area) have fewer thrombolysis-related complications, whereas those with a large thrombus (>1.0 cm diameter or 0.8 cm^2 in area) have a 2.4-fold rate of complications per 1.0 cm^2 increase in size. Factors that identify patients at risk for adverse outcomes of fibrinolytic therapy include active internal bleeding, history of hemorrhagic stroke, recent cranial trauma or neoplasm, diabetic hemorrhagic retinopathy, large thrombi, mobile thrombi, systemic hypertension (>200 mm Hg/120 mm Hg), hypotension or shock, and NYHA class III to IV symptoms.

With mild symptoms due to aortic or mitral valve thrombosis with a small thrombus burden, it is prudent to reassess after several days of intravenous UFH. If valve thrombosis persists, fibrinolysis with a recombinant tissue plasminogen activator dose of a 10 mg IV bolus followed by 90 mg infused IV over 2 hours is reasonable. Heparin and glycoprotein IIb/IIIa inhibitors are held, but aspirin can be continued. A lower tissue plasminogen activator dose of a 20 mg IV bolus followed by 10 mg per hour for 3 hours may be appropriate in some situations. Alternatively, streptokinase may be used with a loading dose of 500,000 IU in 20 minutes followed by 1,500,000 IU over 10 hours. Urokinase is less effective than tissue plasminogen activator or

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streptokinase. If fibrinolytic therapy is successful, it is followed by intravenous UFH until VKA achieves an INR of 3.0 to 4.0 for aortic prosthetic valves and 3.5 to 4.5 for mitral prosthetic valves. A structured institutional protocol with indications, contraindications, and a specific timeline for medication administration and patient monitoring is recommended.

After treatment of the acute thrombotic event, it is important to always determine the adequacy of anticoagulation before the event and ensure that there is meticulous follow-up after the event. The anticoagulation regimen can be increased as outlined in Section 11.5.2.

Supporting References: (609, 610)

Class IIa

2. **Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves (611, 612). *(Level of Evidence: B)***

In nonrandomized, retrospective cohorts of thrombosed mechanical or biological tricuspid valve prostheses, fibrinolysis was as successful in normalization of hemodynamics as surgical intervention. With fibrinolysis of right-sided valve thrombosis, the resultant small pulmonary emboli appear to be well tolerated and systemic emboli are uncommon.

See Online Data Supplement 22 for more information on fibrinolytic therapy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

11.6.3. Intervention: Recommendations

Class I

1. **Emergency surgery is recommended for patients with a thrombosed left-sided prosthetic heart valve with NYHA class III to IV symptoms (610, 611, 613). *(Level of Evidence: B)***

Prompt surgical treatment of a thrombosed prosthetic heart valve is an effective treatment to ameliorate clinical symptoms and restore normal hemodynamics, with a success rate close to 90% in patients who do not have a contraindication to surgical intervention. In contrast, a meta-analysis of 7 studies that included 690 episodes of left-sided prosthetic valve thrombosis showed a success rate for restoring normal valve function of only about 70% in 244 cases treated with fibrinolytic therapy. There was no difference in mortality between surgical and fibrinolytic therapy for left-sided prosthetic valve thrombosis, but in addition to a higher success rate for restoring normal valve function, surgery was associated with lower rates of thromboembolism (1.6% versus 16%), major bleeding (1.4% versus 5%), and recurrent prosthetic valve thrombosis (7.1% versus 25.4%). Although RCTs have not been performed, the weight of the evidence favors surgical intervention for left-sided prosthetic valve thrombosis unless the patient is asymptomatic and the thrombus burden is small.

Supporting References: (605, 613, 614)

Class IIa

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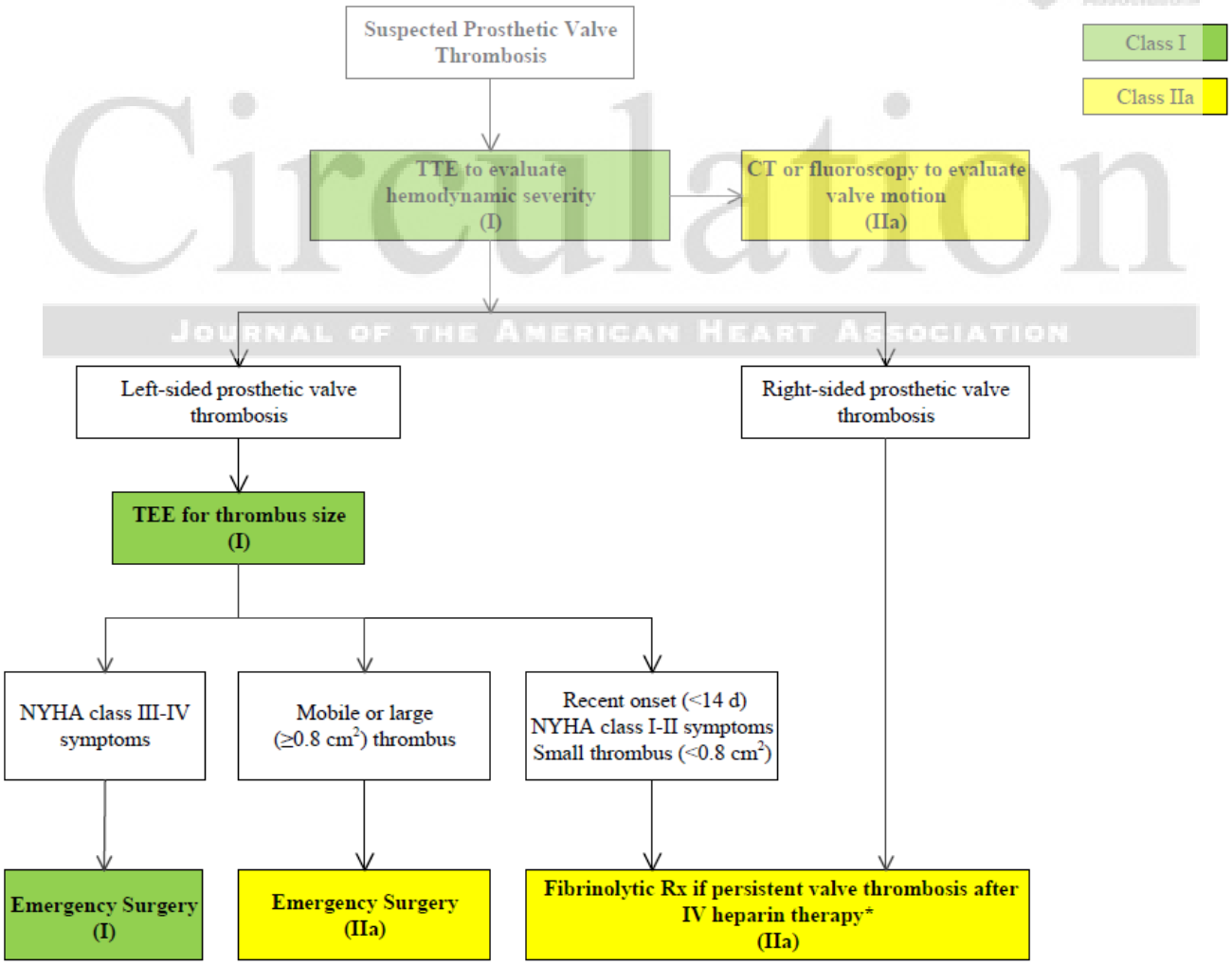
1. **Emergency surgery is reasonable for patients with a thrombosed left-sided prosthetic heart valve with a mobile or large thrombus (>0.8 cm^2) (605, 607, 610). *(Level of Evidence: C)***

Prompt surgical treatment of a thrombosed prosthetic heart valve is associated with a relatively low rate of mortality. In a retrospective study of 106 surgeries for obstructed left-sided prosthetic heart valves, the mortality rate was 17.5% for patients with NYHA class IV symptoms and 4.7% in those patients with NYHA class I to III symptoms. Mortality was similar for removing the thrombus or replacing the entire prosthetic valve. Patients with large, mobile clots that extend beyond the prosthesis are better suited for surgical intervention than fibrinolysis, which is associated with significant risk of systemic embolism. In 1 report, in which patients with small thrombus burden (<0.8 cm^2 on TEE imaging) had minimal thrombolysis-related complications, those with large thrombus burden (≥0.8 cm^2) had a 2.4-fold rate of complications per 1.0 cm^2 increase in size, making surgery the optimal intervention. In patients with recent hemorrhagic stroke, surgery is a better choice because of the bleeding risks associated with fibrinolysis.

Figure 7. Evaluation and Management of Suspected Prosthetic Valve Thrombosis



*See text for dosage recommendations.

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CT indicates computed tomography; IV, intravenous; NYHA, New York Heart Association; Rx, therapy; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

11.7. Prosthetic Valve Stenosis

11.7.1. Diagnosis and Follow-Up

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 valve endocarditis (PVE). Causes of prosthetic valve stenosis that might require reoperation with a mechanical valve include chronic thrombus or pannus impinging on normal leaflet occluder motion; for a bioprosthetic valve, leaflet fibrosis and calcification are the most common causes. Reoperation may also be needed for recurrent thromboembolism, severe intravascular hemolysis, severe recurrent bleeding from anticoagulant therapy, and thrombosed prosthetic valves.

In some patients, the size of the prosthetic valve that can be implanted results in inadequate blood flow to meet the metabolic demands of the patient, even when the prosthetic valve itself is functioning normally. This situation, called "patient-prosthesis mismatch" (defined as an indexed effective orifice area ≤ 0.85 cm^2/m^2 for aortic valve prostheses), is a predictor of a high transvalvular gradient, persistent LV hypertrophy, and an increased rate of cardiac events after AVR. The impact of a relatively small valve area is most noticeable with severe patient-prosthesis mismatch, defined as an orifice area <0.65 cm^2/m^2. Patient-prosthesis mismatch is especially detrimental in patients with reduced LVEF and may decrease the likelihood of resolution of symptoms and improvement in LVEF. Patient-prosthesis mismatch can be avoided or reduced by choosing a valve prosthesis that will have an adequate indexed orifice area, based on the patient's body size and annular dimension. In some cases, annular enlargement or other approaches may be needed to allow implantation of an appropriately sized valve or avoidance of a prosthetic valve. With bileaflet mechanical valves, patterns of blood flow are complex and significant pressure recovery may be present; this may result in a high velocity across the prosthesis that should not be mistaken for prosthetic valve stenosis or patient-prosthesis mismatch.

In patients with bioprosthetic valves who show evidence of prosthetic valve stenosis, TTE is used to monitor the appearance of the valve leaflets, valve hemodynamics, LV size, and systolic function, and to estimate pulmonary pressures. Transthoracic imaging is usually adequate, with TEE imaging reserved for patients with poor-quality images. In patients with mechanical valves, fluoroscopy or CT imaging can be helpful for showing disc motion. CT may also visualize paravalvular pannus formation with either bioprosthetic or mechanical valves.

Supporting References: (527, 528, 544, 615, 616)

11.7.2. Medical Therapy

There are no medical therapies known to prevent bioprosthetic valve degeneration other than those integrated into the valve design. Medical therapy is not effective for treatment of symptoms due to significant prosthetic

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valve stenosis, except with valve thrombosis, but standard medical therapy may help stabilize patients before surgical intervention and may be used for palliative care in patients who are not surgical candidates.

11.7.3. Intervention: Recommendation

Class I

1. **Repeat valve replacement is indicated for severe symptomatic prosthetic valve stenosis. *(Level of Evidence: C)***

The indications for surgical intervention for prosthetic valve stenosis are the same as those for native stenosis of the aortic or mitral valve. Surgery is primarily needed for bioprosthetic valve degeneration. In this situation, the choice of a new valve prosthesis depends on the same factors as those for patients undergoing a first valve replacement. The use of transcatheter valve prostheses to treat bioprosthetic valve stenosis with a "valve-in-valve" approach is promising but is not yet fully validated.

Mechanical valve stenosis is rare and typically due to valve thrombosis or pannus formation. If patient noncompliance contributed to valve thrombosis, it is prudent to consider a bioprosthetic valve at the time of reoperation. With attention to optimal valve selection, a second surgical procedure for significant patient-prosthesis mismatch is rarely needed and should be considered only if a larger prosthetic valve or a valve type with better hemodynamics can be implanted.

11.8. Prosthetic Valve Regurgitation

11.8.1. Diagnosis and Follow-Up

In patients with bioprosthetic valves who show evidence of prosthetic valve regurgitation, TTE is used to monitor the appearance of the valve leaflets, valve hemodynamics, LV size, and systolic function, and to estimate pulmonary pressures. The initial approach is TTE for evaluation of antegrade valve velocities and pressure gradients. However, TEE is essential for evaluation of suspected or known prosthetic mitral valve regurgitation. On TTE imaging, the LA is shadowed by the valve prosthesis, obscuring evidence of prosthetic regurgitation. TEE imaging provides clear images of the left atrial side of the mitral prosthesis and is particularly useful for delineation of the site and severity of paravalvular regurgitation, evaluation of suitability for a percutaneous approach, and guidance during percutaneous closure procedures.

11.8.2. Medical Therapy

Bioprosthetic valve regurgitation is typically due to leaflet degeneration and calcification. There are no medical therapies known to prevent bioprosthetic valve degeneration other than those integrated into the valve design. Pathological regurgitation of a mechanical prosthetic valve is typically due to a paravalvular leak or pannus limiting normal occluder closure. Medical therapy is not effective for treatment of symptoms due to significant prosthetic valve regurgitation, but standard approaches may help stabilize patients before surgical intervention and may be used for palliative care in patients who are not surgical candidates.

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11.8.3. Intervention: Recommendations

Class I

1. **Surgery is recommended for operable patients with mechanical heart valves with intractable hemolysis or HF due to severe prosthetic or paraprosthetic regurgitation (617, 618). *(Level of Evidence: B)***

The indications for surgical intervention for prosthetic valve regurgitation include the same indications for native regurgitation of the aortic or mitral valve. Specifically, indicators are evidence of LV systolic dysfunction, including a low LVEF or progressive LV dilation; the same cut-off points should be used as defined for native valve disease. Paravalvular regurgitation may also result in hemolytic anemia; often this is mild and is managed medically but may be refractory in some patients. Paravalvular regurgitation may be treated by replacing the dysfunctional valve with a new valve or by repairing the paravalvular defect.
Supporting Reference: (619)

Class IIa

1. **Surgery is reasonable for operable patients with severe symptomatic or asymptomatic bioprosthetic regurgitation. *(Level of Evidence C)***

Bioprosthetic valve degeneration results in regurgitation due to leaflet calcification and noncoaptation or leaflet degeneration with a tear or perforation. Even in asymptomatic patients with severe bioprosthetic regurgitation, valve replacement is reasonable due to the risk of sudden clinical deterioration if further leaflet tearing occurs. The choice of type of valve prosthesis in a patient undergoing reoperation depends on the same factors as those for patients undergoing a first valve replacement. The use of transcatheter valve prostheses to treat bioprosthetic valve regurgitation with a "valve-in-valve" approach is promising but is not yet fully validated. Paravalvular regurgitation can also occur with a bioprosthetic valve. New paravalvular regurgitation may be due to IE or suture disruption from mechanical causes. Blood cultures should be obtained when new paravalvular regurgitation is detected.

Class IIa

2. **Percutaneous repair of paravalvular regurgitation is reasonable in patients with prosthetic heart valves and intractable hemolysis or NYHA class III/IV HF who are at high risk for surgery and have anatomic features suitable for catheter-based therapy when performed in centers with expertise in the procedure (620-622). *(Level of Evidence B)***

Surgery is a viable therapeutic option in many patients with symptomatic paravalvular prosthetic regurgitation. However, in some patients, surgery to replace a prosthetic valve with significant paravalvular regurgitation may carry significant operative risk due to the need for reoperation and patient comorbidity. Recent studies have demonstrated clinical success with percutaneous approaches, in which operators use complex catheter techniques and a variety of occluder devices to reduce paravalvular regurgitation. Procedural success rates with percutaneous closure, typically defined by no more than mild residual regurgitation and the absence of death and

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major complications, have been reported to be 80% to 85% in centers with expertise in the procedure. Major complications, nonetheless, occur in 9% of patients, mainly due to vascular injury, cardiac perforation, and bleeding (procedural death, <2%). The degree of residual regurgitation directly affects symptom improvement and survival free of adverse events. Treatment of HF symptoms is more successful than treatment of hemolysis. Due to the complexity of these procedures, consideration should be given to their performance in centers of expertise under the guidance of a multidisciplinary team.

Supporting References: (620-629)

See Online Data Supplement 23 for more information on paravalvular regurgitation (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

12. Infective Endocarditis

See Online Data Supplement 24 for more information on surgical outcomes (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

12.1. IE: Overview

IE has a high mortality rate, even with appropriate antibiotic therapy and surgical intervention, with an in-hospital mortality rate of 15% to 20% and a 1-year mortality rate approaching 40%. The overall incidence of IE is 3 to 10 per 100,000 patient-years, with a higher prevalence in older patients. In underdeveloped countries, IE is most often associated with rheumatic heart disease. In developed countries, IE is increasingly associated with prosthetic valve and intracardiac devices, with a risk of IE 50 times higher in patients with a prosthetic valve compared with the general population. IE also may be associated with intravenous drug use, diabetes mellitus, or immunosuppression. Despite differences in associated risk factors and clinical outcomes, there are few differences in the recommendations for diagnosis and treatment of NVE versus PVE. In this guideline, there is 1 set of recommendations for diagnosis and management of all types of IE. Recommendations for prevention of IE are included in Section 2.

Antimicrobial therapy is the cornerstone of therapy for IE. The specific antimicrobial agents and duration of therapy should be guided by the susceptibility profile of the causative organism. Temporal and geographic variability in causative organisms and antimicrobial susceptibility profiles mandate concomitant management with an infectious disease specialist. Details of specific antimicrobial regimens have previously been published by the AHA, European Society of Cardiology, and British Society for Antimicrobial Chemotherapy and are not repeated in this guideline.

In addition to antibiotic therapy, early surgical intervention is often needed for effective treatment of infection and to manage the sequelae of valve leaflet and paravalvular tissue destruction. Decisions about whether surgical intervention is needed and the optimal timing of intervention are complex. Most of the indications for surgical intervention are the same for NVE and PVE and are included in 1 recommendation for both when possible. Appropriate management of patients with IE requires a Heart Valve Team approach,

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initiated as soon as a diagnosis of probable or definite IE is confirmed, with specialists in cardiology, cardiothoracic surgery, and infectious disease all involved in patient care and decision making.

Supporting References: (52, 279, 630-635)

12.2. Infective Endocarditis

See Online Data Supplement 24 for more information on surgical outcomes (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

12.2.1. Diagnosis and Follow-Up: Recommendations

See Figure 8 for recommendations for imaging studies in NVE and PVE.

Class I

1. **At least 2 sets of blood cultures should be obtained in patients at risk for IE (e.g., those with congenital or acquired VHD, previous IE, prosthetic heart valves, certain congenital or heritable heart malformations, immunodeficiency states, or injection drug users) who have unexplained fever for more than 48 hours (636) *(Level of Evidence: B)* or patients with newly diagnosed left-sided valve regurgitation. *(Level of Evidence: C)***

Blood cultures are positive in 90% of patients with IE. In patients with a chronic (or subacute) presentation, 3 sets of blood cultures should be drawn >6 hours apart at peripheral sites before initiation of antimicrobial therapy. However, this is not feasible or safe in patients with severe sepsis or septic shock. In this situation, at least 2 cultures at separate times should allow for a secure microbiological diagnosis before initiation of antimicrobial therapy. More important than the time interval of the cultures is the observance of strict aseptic technique, avoiding sampling from intravascular lines, and ensuring adequate volume of blood for culture sample. Routine incubation of blood cultures for >7 days is no longer necessary in the era of continuous-monitoring blood culture systems and nonculture-based technology. In the 10% of patients with culture-negative endocarditis, serologic testing to identify the etiologic agent is appropriate.

Supporting References: (52, 637-641)

Class I

2. **The Modified Duke Criteria should be used in evaluating a patient with suspected IE (Tables 24 and 25) (642-645). *(Level of Evidence: B)***

The Modified Duke Criteria (Tables 24 and 25) have been well validated in comparison to surgical or autopsy findings and in clinical outcomes in numerous studies in a wide spectrum of patients, including children, the elderly, prosthetic valve recipients, injection drug users, and nondrug users, as well as patients in both primary and tertiary care settings. Clinical judgment and infectious disease specialty guidance is essential when deciding on the type and duration of antibiotic therapy when these criteria suggest possible IE and in patients with unusual clinical presentations or culture-negative endocarditis. About three fourths of patients with IE are diagnosed within 30 days of the onset of infection, so that classic clinical features, such as embolic or vasculitic skin lesions, renal disease due to immune complex deposition, and immunologic abnormalities of IE, are often

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absent. In these cases, maintaining a high level of clinical suspicion to the possibility of IE in patients who are susceptible is paramount.

Supporting References: (644, 646-650)

Table 24. Diagnosis of IE According to the Proposed Modified Duke Criteria

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

IE indicates infective endocarditis. (642, 644)

Table 25. Major and Minor Criteria in the Modified Duke Criteria for the Diagnosis of IE

Major Criteria
1. Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci*, *Streptococcus bovis*, HACEK group (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp., and *Kingella kingae), Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: • At least 2 positive cultures of blood samples drawn 12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn at least 1 h apart) • Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
2. Evidence of endocardial involvement
• Echocardiogram positive for IE defined as follows: o Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation o Abscess; or o New partial dehiscence of prosthetic valve • New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor Criteria
1. Predisposition, predisposing heart condition, or injection drug use
2. Fever, temperature >38° C (100.4° F)
3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

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5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause IE.

C indicates Celsius; F, Fahrenheit; IE, infective endocarditis; spp, species; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. (642, 644)

Class I

3. **Patients with IE should be evaluated and managed with consultation of a multispecialty Heart Valve Team including an infectious disease specialist, cardiologist, and cardiac surgeon. In surgically managed patients, this team should also include a cardiac anesthesiologist (651).** ***(Level of Evidence: B)***

The diagnosis of IE can still be difficult and is frequently delayed, which may cause progressive and potentially irreparable structural damage to the heart and other organ systems secondary to vascular-embolic and immunologically mediated events. The in-hospital mortality rate for patients with IE remains high (15% to 20%), with 1-year mortality, even in the current therapeutic era, approaching 40%. Additionally, stroke (16.9%), embolization other than stroke (22.6%), HF (32.3%), intracardiac abscess (14.4%), and the need for surgical therapy (48.2%) remain common.

The optimal treatment and potential timing of invasive strategies in these patients can be quite challenging in the individual patient. Patients with suspected IE are most optimally managed in an environment that coordinates management of specialists well attuned to various organ systems, pathological processes, and potential treatment modalities involved. Cardiologists provide expertise in diagnosis, imaging, and clinical management; infectious disease specialists provide expertise in identification of the causative organism and the choice and duration of antimicrobial therapy; cardiac surgeons are essential for decisions about timing of surgical intervention as well as the procedure itself; and anesthesiologists are essential for peri- and intraoperative diagnosis and management. Because the urgent/emergency need for surgical intervention can arise rapidly, it is strongly recommended that these patients be cared for in centers with immediate access to cardiac surgery during the initial observation stages of the disease. With the emerging use of telemedicine, it may be reasonable to manage patients with lower-acuity IE in a center without on-site multispecialty care by telecommunication with a Heart Valve Team and infectious disease specialists. Rapid transfer of the patient should also be available if the need arises. IE is a disease that is continually changing with new high-risk patients, new diagnostic procedures, the involvement of new microorganisms, and new therapeutic approaches. Despite knowledge of these changes and considerable improvements in diagnostic and therapeutic strategies, IE is still a potentially debilitating or fatal disease. Patients affected by the disease are often older and sicker, and the comorbidity rate is high.

Supporting References: (652-654)

Class I

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4. **TTE is recommended in patients with suspected IE to identify vegetations, characterize the hemodynamic severity of valvular lesions, assess ventricular function and pulmonary pressures, and detect complications (655-659).** ***(Level of Evidence: B)***

The presence of valvular vegetation is a major criterion in the diagnosis of IE. TTE has a sensitivity between 50% and 90% and a specificity >90% for detection of vegetations in NVE. TTE has a sensitivity of only 36% to 69% in PVE, but TTE still has a role in these patients for detection and quantitation of valve dysfunction (even in the challenging situation of regurgitation in the mechanical prosthetic mitral valve, for which a proximal convergence zone may provide important evidence for a paravalvular leak), evaluation of ventricular size and systolic function, and estimation of pulmonary pressures. TTE exhibits superior imaging over TEE for the anterior aspect of a prosthetic aortic valve, which is commonly shadowed by the valve on TEE. TTE also allows measurement of aortic transvalvular velocity/gradient, which is not always possible on TEE. Although TTE will not definitely exclude vegetations or abscesses in IE, it can identify very high-risk patients and establish the diagnosis as well as guide early treatment decisions (Figure 8).

Supporting References: (655, 660-664)

Class I

5. **TEE is recommended in all patients with known or suspected IE when TTE is nondiagnostic, when complications have developed or are clinically suspected, or when intracardiac device leads are present (662, 665-672).** ***(Level of Evidence: B)***

The sensitivity of TEE in NVE ranges from 90% to 100%, with sensitivity ranges slightly lower in PVE. The positive predictive value for TEE in both NVE and PVE is 90%. TEE is superior to TTE in the visualization of both vegetations and perivalvular complications, which can be anatomic or hemodynamic in nature. Examples of such complications include valve perforation, abscesses, and pericardial effusion. Hemodynamic complications may include valve regurgitation, fistulae, and intracardiac thrombi. TEE is now considered the most reliable noninvasive test for defining this disease. However, it may not differentiate between active and healed vegetations and may not discriminate between thickened valves or valvular nodules and vegetations. TTE and TEE are complementary for the comprehensive evaluation of hemodynamics and anatomy in patients with IE. Because TEE has a higher sensitivity in detecting anatomic complications, it should be used as an adjunct in patients with echocardiographic features of IE on TTE to rule out the presence of findings such as abscesses, which may alter the therapeutic approach to the management of the patient. TEE also serves a vital role in reassessment of patients with known IE with suspected clinical complications as well as a guiding tool in the intraoperative assessment and management of the IE patient.

The number, type, and timing of repeat examinations depend on the clinical presentation and course as well as the virulence of the microorganism. Vegetation size at diagnosis has clearly identified a higher risk of death in prospective studies. Additionally, 1 study has shown that failure to decrease vegetation size with antibiotic treatment was associated with an increased risk of embolism. Another study demonstrated that most vegetations (83.8%) remain constant in size under therapy and that this does not worsen prognosis. In this study,

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both increase of vegetation size under antibiotic therapy (observed in 10.5% of patients with IE) and reduction of vegetation size under therapy were associated with an increased embolic risk. Thus, increasing vegetation size under therapy must be considered a risk factor for new embolic events, whereas unchanged or reduced vegetation size under therapy may be more difficult to interpret.

Compared with TTE, TEE is more sensitive for detection of vegetations and thrombi associated with device leads. There are emerging data that intracardiac echocardiography may be an increasingly useful tool to diagnose vegetations that may be present on right-sided pacemaker leads. It has shown superior sensitivity over TEE in identifying these lesions.

Supporting References: (664, 670, 673-681)

Class I

6. **TTE and/or TEE are recommended for reevaluation of patients with IE who have a change in clinical signs or symptoms (e.g., new murmur, embolism, persistent fever, HF, abscess, or atrioventricular heart block) and in patients at high risk of complications (e.g., extensive infected tissue/large vegetation on initial echocardiogram or staphylococcal, enterococcal, or fungal infections) (679, 682).** ***(Level of Evidence: B)***

HF, perivalvular extension, and embolic events represent the 3 most frequent and severe complications of IE. They are also the 3 main indications for early surgery, which is performed in almost 50% of cases. If signs or symptoms consistent with any of these complications exist, there should be a very low threshold for repeat imaging in these patients. TEE may miss initial paravalvular abscesses, particularly when the study is performed early in the patient's illness. In such cases, the incipient abscess may be seen only as nonspecific paravalvular thickening, which on repeat imaging across several days may become recognizable as it expands and cavitates. Similarly, paravalvular fistulae and pseudoaneurysms develop over time, and negative early TEE images do not exclude the potential for their development. For patients who have IE that was diagnosed by clinical, microbiological, or surgical criteria but for whom results of initial TEE were false-negative, repeated TEE has often demonstrated vegetative IE. Thus, it appears that a single negative TEE study cannot rule out underlying IE and that a repeat TEE study should be performed when a suspicion of persistence of infection remains or if complications ensue. Conversely, in the absence of clinical deterioration or new signs/symptoms, routine follow-up echocardiography is probably of only limited clinical utility.

Supporting References: (52, 630, 665, 683-685)

Class I

7. **Intraoperative TEE is recommended for patients undergoing valve surgery for IE (686, 687).** ***(Level of Evidence: B)***

Intraoperative TEE during cardiac surgery plays an important role in the evaluation and quality control of a large variety of pathologies. Clinical and echocardiographic characteristics may change during an episode of IE because of the prolonged active phase and fluctuating course of this disease. Even if preoperative TEE has been

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performed, the possibility of vegetation change/embolization or extension of the infectious process beyond the valve tissue may occur. In addition, other valves may become involved as the disease timeline progresses. Intraoperative TEE has been invaluable for baseline reassessment of anatomical/hemodynamic changes that may occur in the interval between the diagnostic echocardiogram and the time of surgery. TEE is also an important monitoring tool for evaluation of operative complications such as air emboli and an important adjunct to ensure the quality of the intended surgical result.

Supporting References: (688, 689)

Class IIa

1. **TEE is reasonable to diagnose possible IE in patients with *Staphylococcal aureus* bacteremia without a known source (690-692). *(Level of Evidence: B)***

IE in patients with *Staphylococcal aureus (S. aureus)* bacteremia frequently involves normal cardiac valves and is seldom accompanied by the physical stigmata of IE, rendering the diagnosis of the disease difficult. Reliance on physical examination findings and clinical stigmata is likely to result in underdiagnosis of *S. aureus* IE in a large number of cases. TEE is cost-effective to guide duration of therapy in patients with intravascular catheter-associated *S. aureus* bacteremia, patients with intracardiac electronic devices, or other patients at higher risk for IE (including those with previous prosthetic valve surgery) or associated complications.

Despite early diagnosis and appropriate therapy, IE following *S. aureus* bacteremia is frequently associated with disabling and life-threatening sequelae. The overall mortality of *S. aureus* IE ranges from 19% to 65%. Other complications include HF (20% to 50%), paravalvular cardiac abscesses (30% to 40%), neurological manifestations (30%), and systemic embolization (40%).

Supporting References: (652, 677, 693, 694)

Class IIa

2. **TEE is reasonable to diagnose IE of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur (695, 696). *(Level of Evidence: B)***

When compared with NVE, PVE is characterized by a lower incidence of vegetations (especially in mechanical prostheses) and a higher incidence of annular abscess and other paravalvular complications. Because cardiac auscultation may also be less revealing in PVE and because ordinarily less virulent organisms may cause more anatomic destruction before culture or serological detection, it is important to use TEE early in these high-risk patients. TEE has a lower sensitivity in detecting prosthetic IE when compared with TEE detection rates in NVE, so the importance of comparing serial echocardiographic studies is paramount to making the diagnosis.

Supporting References: (697, 698)

Class IIa

3. **Cardiac CT is reasonable to evaluate morphology/anatomy in the setting of suspected paravalvular infections when the anatomy cannot be clearly delineated by echocardiography (678, 699-701). *(Level of Evidence: B)***

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Electrocardiographic-synchronized, multidetector-row CT is emerging as an important tool for noninvasive cardiac assessment and may be helpful in evaluating complications of IE. CT may also be indicated in right-sided IE to demonstrate the presence of septic pulmonary infarcts and abscesses. Although CT is less accurate than TTE and TEE for identifying valvular vegetation and valvular perforations, CT is useful for evaluating patients with equivocal findings on TEE and for evaluating complications in patients with suspected myocardial, pericardial, and coronary sinus extension of the infectious process. CT can also more sensitively detect paravalvular abscess involvement and evaluate extent and anatomic consequences of pseudoaneurysms and their relationship to adjacent structures. CT imaging is particularly useful in preoperative evaluation of patients with aortic valve IE to evaluate coronary artery and aortic involvement.

In suspected PVE, cardiac CT is less affected by the shadowing of mechanical valves or bioprosthetic valve sewing rings than ultrasound. CT also allows evaluation of motion of mechanical valve occluders and provides visualization of thrombus or infective material limiting valve occluder motion. Additional imaging modalities such as cardiac valvular fluoroscopy can be an adjunct to other clinical and imaging information to detect the presence of obstructive disease of mechanical prosthetic valves affected by IE. Normative values for the opening and closing angles are known for the common valves available for patient use. A combination of cineradiography and echocardiography makes it possible to provide an accurate and detailed determination of the degree and extent of valvular obstruction that may accompany mechanical PVE.

Supporting References: (699, 702-706)

Class IIb

1. **TEE might be considered to detect concomitant staphylococcal IE in nosocomial *S. aureus* bacteremia with a known portal of entry from an extracardiac source (663, 707, 708). *(Level of Evidence: B)***

Because the frequency of IE among patients with *S. aureus* bacteremia is reported to be approximately 30%, with many cases not being clinically suspected, TEE should generally be pursued in the setting of *S. aureus* bacteremia to rule out IE. Even in *S. aureus* bacteremia from a known extracardiac source, such as an infected joint or joint prosthesis, TEE might be considered. given known cases of seeding of valve tissue in this type of setting. Possible exceptions are patients who have no underlying cardiac predisposing conditions or clinical signs of IE whose fever and bacteremia resolve within 72 hours after removal of a likely infected focus (such as intravascular catheter removal). In the absence of 1) prolonged bacteremia >4 days, 2) a permanent intracardiac device, 3) hemodialysis dependency, and 4) spinal infection or nonvertebral osteomyelitis, the risk of IE is relatively low, and routine TEE may not be necessary.

Supporting References: (663, 691, 692, 709)

Figure 8. Recommendations for Imaging Studies in NVE and PVE

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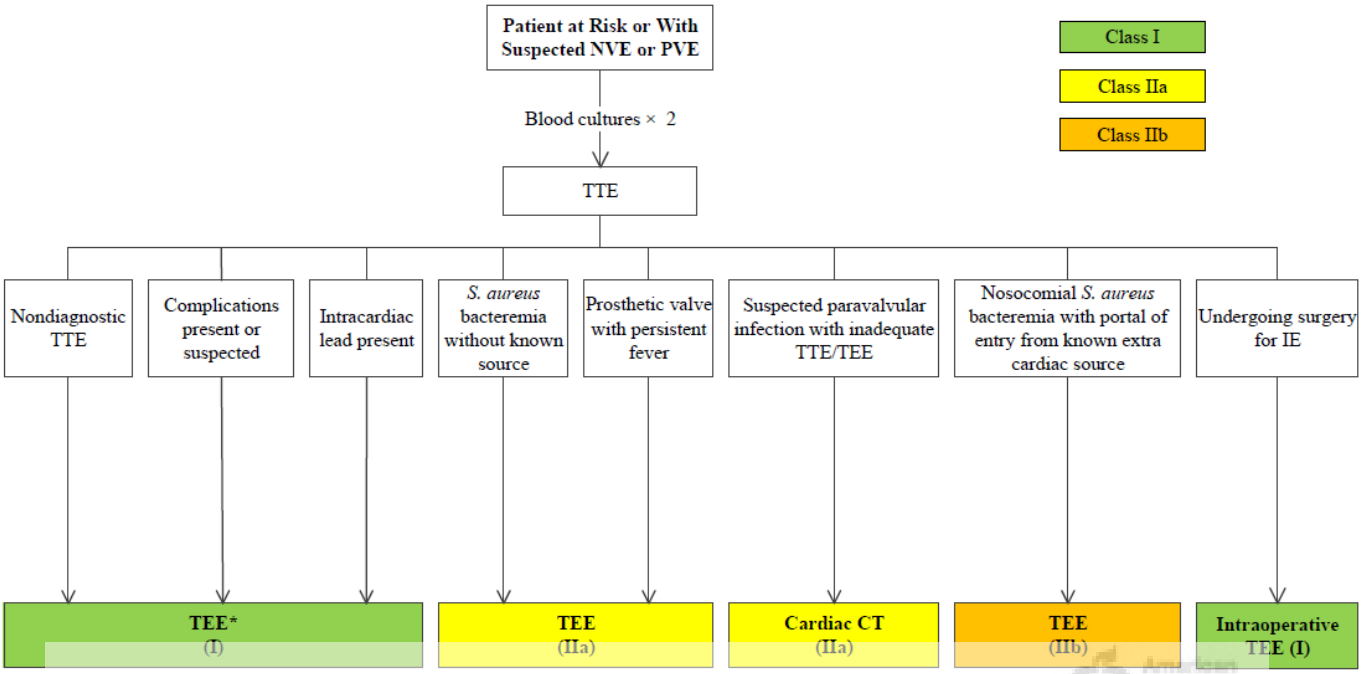

*Repeat TEE and/or TTE recommended for reevaluation of patients with IE and a change in clinical signs or symptoms and in patients at high risk of complications.

CT indicates computed tomography; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; *S. aureus*, *Staphylococcus aureus*; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

12.2.2. Medical Therapy: Recommendations

See Online Data Supplement 24 for more information on surgical outcomes (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

1. **Appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained with guidance from antibiotic sensitivity data and infectious disease consultants (636). *(Level of Evidence: B)***

Optimal treatment of IE is based on the appropriately timed initiation of antimicrobial therapy that is effective against the specific infective organism involved. Empirical therapy may be necessary in patients with septic shock or who show high-risk signs on presentation; however, targeted antimicrobial therapy guided by minimum inhibitory concentration is the goal. The minimum inhibitory concentration is used to determine the antibiotic dosage that the patient will receive and the type of antibiotic used and can lower the opportunity for microbial resistance to specific antimicrobial agents. Prompt use of antibiotics significantly reduces the incidence of emboli in patients with IE. Duration of therapy needs to be guided by those with expertise in the field of antibiotic therapy. Although no RCTs have been performed with the use of antibiotic therapy in IE, the mortality rate before the antibiotic age neared 100%. Despite advances in knowledge of mechanism of therapeutic approaches to treating infections and despite a significant expansion of the antimicrobial armamentarium, the emergence of resistant organisms has led to continued complexity in the approach to patients with systemic infections. Antimicrobial therapy for NVE and PVE should be guided by the

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susceptibility profile of the causative organism. Specific antimicrobial regimens, depending on the causative microorganism, have been published by the British Society for Antimicrobial Chemotherapy and the AHA. Given the ever-changing spectrum of antimicrobial sensitivity, as well as regional and site-specific differences in antimicrobial susceptibility profiles, concomitant management with the assistance of a consultant thoroughly familiar with these patterns is imperative.

Supporting References: (633, 634, 636, 710-713)

Class IIa

1. **It is reasonable to temporarily discontinue anticoagulation in patients with IE who develop central nervous system symptoms compatible with embolism or stroke regardless of the other indications for anticoagulation (714-719). *(Level of Evidence: B)***

There are several potential mechanisms of stroke in patients with IE, including hemorrhagic transformation of an ischemic infarct, septic erosion of an arteritic vessel without aneurysm formation, and rupture of a mycotic aneurysm. Approximately 15% to 35% of all patients with IE develop clinically evident systemic emboli. If more sensitive tests such as cerebral magnetic resonance imaging are used, a much higher proportion of patients with IE have evidence of emboli (≥30%). The most common cause of stroke in patients with IE in the modern antimicrobial era is a septic embolus resulting in ischemia, often followed by hemorrhagic transformation. Anticoagulant therapy may increase the risk of an embolic infarct converting to a hemorrhagic infarct. Hemorrhagic transformations can occur up to 11 days after an initial infarct. On the other hand, the longer anticoagulation is withheld, the higher the chance of recurrent embolization or valve dysfunction in patients with PVE. The beneficial or deleterious effect of anticoagulation in patients with IE is determined by a multitude of clinical, bacteriological, radiological, and echocardiographic variables that may tilt the balance of the risk toward early recurrent stroke or intracranial hemorrhage. Patients with IE and a cerebral embolism or stroke should be referred to a center with a multispecialty Heart Valve Team. A specialist in the field of neurology and/or neuroradiology should be added to this team when the complication of stroke arises in IE. The risk of bleeding complications should be included in the assessment of patients with IE receiving anticoagulation treatment.

Supporting References: (12, 720-726)

Class IIb

1. **Temporary discontinuation of VKA anticoagulation might be considered in patients receiving VKA anticoagulation at the time of IE diagnosis (715, 727-730). *(Level of Evidence: B)***

In patients with NVE, routine use of VKA is not recommended unless a separate indication exists. There is no conclusive evidence that prophylactic use of VKA anticoagulation reduces the incidence of emboli in patients with NVE who have no other indication for anticoagulation.

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Alternatively, for patients already receiving anticoagulation with VKA or aspirin for other evidence-based indications at the time of diagnosis with IE, there is little information on the risks and benefits of continued anticoagulation therapy. Continuing anticoagulant therapy in the face of IE potentially increases the risk of hemorrhagic transformation of an embolic stroke or accentuation of bleeding from septic arteritis or mycotic aneurysms should they occur. The evidence and propensity of expert consensus would suggest that VKAs be discontinued at the time of initial presentation with IE secondary to the combined risk of bleeding from potentially urgent invasive procedures and the risk of developing hemorrhagic stroke. Early surgery is required in roughly 50% of patients with PVE. Although there is no evidence regarding the use of bridging therapy with intravenous or subcutaneous anticoagulant therapy while patients are off VKAs, studies indicate that there is increased risk of hemorrhagic stroke in patients on intravenous UFH during the acute phase of acute IE. It should be noted that the strength of this evidence is low, and some institutional practices continue VKA anticoagulation until an invasive procedure is deemed a definitive necessity or until a neurological complication develops or is noted on imaging studies. Decisions about continued anticoagulation and antiplatelet therapy should ultimately be directed by the patient's consulting cardiologist and cardiothoracic surgeon in consultation with a neurology specialist if neurological findings are clinically present or noted on imaging. Although there is no strong evidence base for screening neurological imaging studies and their potential impact on management, the data are strong that subclinical neurological abnormalities are common, occurring in 25% of patients with IE and *S. aureus* and up to 55% of critically ill patients with IE. In patients with valvular or nonvalvular indications for continued use of VKAs, strong consideration should be given to cerebral magnetic resonance imaging to evaluate for subclinical cerebrovascular complications to help guide anticoagulation management. Novel oral anticoagulants have no indication for VHD.

In patients with IE, routine antiplatelet therapy is not recommended unless a separate indication exists. There is no evidence that routine use of aspirin in the setting of IE reduces risk of embolic stroke in patients who are already receiving antibiotic therapy. However, large retrospective studies have suggested that embolism associated with IE occurs less frequently among patients who have received continuous daily antiplatelet therapy for other indications before the diagnosis of IE.

Supporting References: (12, 728-735)

Class III: Harm

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

Two sets of blood cultures are the minimum for a secure microbiological diagnosis of IE. The leading cause of "culture-negative IE," which can be a significant clinical conundrum, is the use of antibiotics before blood cultures are obtained. Negative blood cultures in the setting of IE can delay diagnosis by slowing other serological and polymerase chain reaction assessments; therefore, it can delay definitive treatment of the patient as well as impair determination of antimicrobial treatment duration. The identification of the causative pathogen

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will improve the specificity of the therapeutic regimen and may significantly improve patient outcome. *S. aureus* is the most common pathogen responsible for PVE but still accounts for only 23% of cases. Antibiotic therapy is most effective if the identity and sensitivities of the responsible organism are known.

Supporting References: (724, 736, 737)

12.2.3. Intervention: Recommendations

See Figure 9 for diagnosis and treatment of IE and Online Data Supplement 24 for more information on surgical outcomes (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

1. **Decisions about timing of surgical intervention should be made by a multispecialty Heart Valve Team of cardiology, cardiothoracic surgery, and infectious disease specialists (651). *(Level of Evidence: B)***

The in-hospital mortality rate for IE is high, at 15% to 20%, with 1-year mortality approaching 40%. Given those rates and the complexities and uncertainties about surgical timing/indications related to comorbid conditions in many of these patients, it is recommended that patients with IE be managed in an environment with ready access to specialists in the fields of cardiology, cardiothoracic surgery, and infectious disease. Cardiothoracic surgical consultation should be obtained rapidly after the diagnosis of IE. A risk-scoring system using the STS database has been developed to predict risk of surgery in patients with IE to help better counsel patients and more objectively define risks of surgery. One trial noted that even when surgery is indicated, women were less likely to undergo a surgical procedure than men (26% versus 47%) and that women had higher in-hospital and 1-year mortality rates than men despite similar comorbidities. To prevent subjective bias in decision making for patients, it is recommended that hospitals use system policies to ensure best practices in patients with IE.

Supporting References: (738-740)

Class I

2. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE who present with valve dysfunction resulting in symptoms of HF (741-746). *(Level of Evidence: B)***

Death may occur suddenly in patients with endocarditis-induced HF, particularly if the aortic valve is involved. The ICE-PCS (International Collaboration on Endocarditis-Prospective Cohort Study) has reported a 21% in-hospital mortality rate in patients with IE with HF treated with surgery versus a 45% mortality rate in those who were medically treated. One-year mortality in this study was 29.1% in patients undergoing valvular surgery versus 58.4% in those not undergoing surgery. In complicated left-heart NVE, 4 baseline features have been independently associated with 6-month mortality: abnormal mental status, moderate-to-severe HF, bacterial etiology other than *Viridans streptococci*, and medical therapy without valve surgery. This risk stratification system has been validated in a separate cohort, and similar findings have been reproduced in both retrospective propensity studies and prospective studies. Prompt surgical consultation should be obtained in all cases of IE to

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assist with assessment of the need for surgical treatment and to help judge the timing of surgery. Further prospective randomized studies with large study populations are necessary to more precisely evaluate the optimal timing of surgery in patients with NVE.

Reinfection after prosthetic valve surgery (which occurs in 5% to 10% of patients, with a significant percentage of these being injectable drug users) is low relative to the risk of no surgery in patients with hemodynamic and microbial indications for surgery. Repair rather than replacement of a valve is always best; however, such repairs are possible in only a minority of cases, such as when a leaflet perforation occurs without extensive leaflet destruction or annular involvement. PVE is clearly associated with both higher mortality rates (especially if associated with a new murmur, HF, or severe valvular dysfunction or if the infectious microbe is staphylococcal or fungal) and higher post-treatment HF-related disability. Most surgical series report a surgical rate of nearly 50% in patients with PVE. Up to 20% more would benefit from surgery if it were not for an already developed catastrophic complication. Surgical debridement and replacement of the infected prosthetic valve leads to significantly lower mortality (23%) compared with medical therapy alone (56%). Improved outcome was seen for the surgical group even when controlling for severity of illness at time of diagnosis. In a series of 1,025 patients with PVE, early surgery did not reduce in-hospital or 1-year mortality when adjusted for the propensity to operate and the effect of survivor bias. However, subgroup analysis indicated that patients with the strongest indications for surgery (new left-sided valve regurgitation, paravalvular abscess or fistula, prosthetic valve dehiscence, or HF) did have a lower 1-year mortality rate with early surgery (27.9% versus 50.0%; p=0.007).

PVE is classified into "early-," "intermediate-," and "late-" onset PVE. Early-onset PVE is defined as occurring within the first 60 days of surgery and is typically associated with healthcare–acquired infection, with the most common microbe during this time frame being *S. aureus*. Intermediate-onset PVE occurs between 60 and 365 days after surgery and is associated with a mix of both healthcare–acquired infection and community-acquired infection. The most common microbe implicated in intermediate-onset PVE is coagulase-negative *Staphylococcus*. Two thirds of all reported cases of PVE occur within the first year of valve surgery. Late-onset PVE is defined as occurring >1 year after surgery. Although *S. aureus* and coagulase-negative *Staphylococcus* remain important infecting agents, the late-onset PVE microbial spectrum more closely resembles that of NVE. *Supporting References:* (635, 724, 747-751)

Class I

3. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with left-sided IE caused by *S. aureus*, fungal, or other highly resistant organisms (746, 752-758). *(Level of Evidence: B)***

In the United States, 34% of NVE cases are due to *S. aureus*. Compared with patients with IE due to other organisms, patients with *S. aureus* IE were significantly more likely to die (20% versus 12%), experience an embolic event (60% versus 31%), have a central nervous system event (20% versus 13%), and not undergo

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surgery (26% versus 39%). Although mortality rates are lower in patients with methicillin-sensitive *S. aureus*, the rate of embolic events is even higher than that of methicillin-resistant *S. aureus*. Factors involved in the higher modern rates of *S. aureus* IE are a low prevalence of rheumatic heart disease (therefore an older, less immunocompetent population with underlying degenerative VHD), a larger population of hemodialysis patients, an increasing diabetic population, and a higher rate of prolonged use of an intravascular device. In hospital-acquired IE, the mortality rate has been reported to be 2 times that of community-acquired IE, largely due to resistant staphylococcal and enterococcal species. Certain pathogens, such as *Pseudomonas aeruginosa*, *Brucella*, fungi, and gram-positive cocci (especially those that are resistant to beta-lactam antibiotics or vancomycin) are extremely difficult to cure with medical therapy alone. Many of these organisms are also prone to abscess/fistula formation and other cardiac tissue destruction, which cannot be effectively treated with medical therapy alone. Despite high-quality imaging using 2D and even 3D TEE, false-negative findings for intracardiac abscess are as high as 60%. Similar to studies in *S. aureus* IE, the mortality rate is significantly lower in patients treated with antifungal agents combined with surgery compared with those treated with antifungal agents alone (42% versus 59%).

An important distinction is made for injectable drug users. When *Staphylococcus* is the bacteria, death occurs in <5% of patients with right-sided NVE; however, in left-sided NVE with the same organism, death ensues in 20% to 30% of cases. In injectable drug users with NVE, *Enterococcus* sp carries a mortality rate of 15% to 25%. *Pseudomonas aeruginosa*, Enterobacteriaceae, and fungi, though rare, carry an overall mortality rate of >50% in this population. Coexisting conditions that increase mortality in injectable drug users include HF, neurological events, renal failure, and symptomatic HIV infection. Given the high nonsurgical cure rates of right-sided IE combined with the significant concern of reinfection of prosthetic material in surgical intervention, an even more coordinated effort of surgical and nonsurgical experts in management of NVE is necessary for injectable drug users.

Staphylococcal PVE has been associated with a mortality rate as high as 70%. Given the difficulty in eradicating *Staphylococcus* spp when foreign and avascular material are involved in the infection, survival rates are significantly higher in patients who undergo surgical debridement and have the infected valve removed and replaced. Mortality rates remain higher in this group of patients whether treated surgically or not when compared with every other category of IE aside from fungal infections. *Pseudomonas aeruginosa* and multiresistant enterococci, for which there is no synergistic bactericidal regimen, are also less amenable to medical therapy.

Supporting References: (652, 724, 747, 753, 759-766)

Class I

4. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (746, 767-771). *(Level of Evidence: B)***

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Abscess of the native valves or paravalvular structures with or without extension to the cardiac conduction system is a life-threatening complication that cannot be cured with antibiotic therapy alone. Early recognition and institution of appropriate medical and surgical therapy is necessary for patient survival. Complete heart block in IE usually occurs secondary to extension of infection into the atrioventricular node. Heart block is most commonly associated with aortic valve IE, given the high prevalence of paravalvular extension and the proximity of the conduction system to the valve (although it has also been reported in mitral and tricuspid valve IE) and is associated with an increased risk for sudden cardiac death and more severe anatomical destruction of cardiac tissues. Extensive perivalvular infections (to include annular/aortic abscesses and destructive penetrating lesions/fistulae) respond poorly to medical therapy and are associated with a mortality rate of ≥40%. Patients with paravalvular abscess are typically very ill by the time they are referred for surgery. Even so, the long-term results of surgery are very satisfactory, with an actuarial survival rate of 75±6% at 5 years. Freedom from recurrent IE has been reported to be 76% at 8 years. The 2 primary objectives of surgery are total removal of infected tissues and reconstruction of functional anatomy. Surgical series have shown that the surgical results are more related to a surgeon's ability to remove all infected tissues than to the type of valve used for a replacement.

Patients with PVE complicated by paravalvular invasion, as manifested by intracardiac abscesses, fistulae, or heart block, experience high mortality rates and are rarely cured by medical treatment alone. By contrast, surgical series have reported surgical survival rates of 71% in this high-risk group.

Supporting References: (724, 772-775)

Class I

5. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) for IE is indicated in patients with evidence of persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy (746, 756, 757, 776-778).** ***(Level of Evidence: B)***

Blood cultures will typically become negative after 48 hours of appropriate antimicrobial therapy; however, in methicillin-resistant *S. aureus* and other resistant organisms, it may take up to a week for cultures to become negative. An ongoing infection despite antibiotic therapy is common with aggressive microorganisms, abscess formation, or large vegetations. In some patients, the only evidence of persistent infection is an elevated white blood cell count or fevers that persist longer than 5 to 7 days. In patients with persistent bacteremia despite appropriate susceptibility-based therapy, the clinician must consider surgical adjunctive therapy based on multispecialty input and guidance from serial TEE and other imaging data. Detection of abscess by TEE can be missed in the presence of calcification in the posterior mitral annulus or because of echocardiography artifact from prosthetic material. CT imaging may be helpful in this situation. Early surgery has been shown to improve outcome in patients with an abscess. Additionally, patients with persistent sepsis are at high risk of developing multiorgan failure, and surgery may be needed in these patients to debride infected/necrotic tissues to effectively eradicate the infection. Predictors of in-hospital mortality in patients with PVE include older age, healthcare-

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associated infection, *S. aureus* infection, HF, stroke, intracardiac abscess, and persistent bacteremia. Some caution is advised in patients who develop recurrent fever after an initially successful response to antibiotics, because the fever could be explained by other reasons than the endocarditic valve.

Supporting References: (724, 746, 747, 777, 779)

Class I

6. **Surgery is recommended for patients with PVE and relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequently negative blood cultures) without other identifiable source for portal of infection. *(Level of Evidence: C)***

TEE has a reduced sensitivity for detection of abscess in patients with prosthetic valves. If there is suspicion by a team of cardiologists, cardiothoracic surgeons, and infectious disease specialists that relapsing infections may be due to incomplete sterilization of valvular or paravalvular tissue secondary to a deep tissue infection, it is reasonable to consider surgery in this situation. In the absence of other indications for intervention, such as severe valve dysfunction or a resistant organism, the timing of surgical intervention cannot be strictly defined in these situations. Because the possibility of "reseeding" a prosthetic valve has been reported in the setting of infection from an origin separate from the heart, careful assessment for the possibility of reintroduction of an infectious microbe from another portal should be thoroughly ruled out in these instances before consideration of cardiac surgical reintervention.

Supporting Reference: (746)

Class I

7. **Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is indicated as part of the early management plan in patients with IE with documented infection of the device or leads (780-783). *(Level of Evidence: B)***

Complete device and lead removal is recommended for all patients with cardiac device infection, even if evidence for infection appears to be limited to the generator pocket site. A prospective cohort study using data from the ICE-PCS showed that among patients with cardiac device IE, the rates of both concomitant valve infection and mortality are high, particularly if there is valve dysfunction. Optimal therapy for cardiac device IE combines complete device extraction and a prolonged course of parenteral antibiotics. A proportional hazards regression analysis showed a survival benefit at 1 year for device removal during the initial hospitalization; 28 of 141 patients (19.9%) who underwent device removal during the index hospitalization had died at 1 year versus 13 of 34 (38.2%) who did not undergo device removal (HR: 0.42; 95% CI: 0.22 to 0.82).

Supporting References: (681, 784-786)

Class IIa

1. **Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients with valvular IE caused by *S. aureus* or fungi, even without evidence of device or lead infection (780-783). *(Level of Evidence: B)***

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The likelihood of underlying cardiac device infection in a patient with *S. aureus* bacteremia is relatively high (approximately 30% to 40%) and is also likely in patients with fungal valvular IE. In patients with a normal pocket site, it is difficult to determine if the device should be removed. If there is evidence of valvular endocarditis on TEE, then the device should be removed. If there is a lead mass without a valve lesion, device removal has been advocated by some based on "lead endocarditis." However, the writing committee noted that the likelihood of finding a clot on a lead in noninfected patients can range from 1% to 50% of patients undergoing TEE.

The likelihood of underlying cardiovascular implantable electronic device infection in someone with bacteremia due to gram-negative bacilli is much less. Therefore, if the pocket site appears normal, device removal is generally not required for an initial episode of bacteremia.

Supporting References: (781, 785, 787)

Class IIa

2. **Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients undergoing valve surgery for valvular IE. *(Level of Evidence: C)***

In patients with an intracardiac lead who are undergoing prosthetic valve replacement for valvular IE, the device and lead might serve as a nidus for recurrent infection because infection of the leads may be present even without visible vegetations. Removal of the entire device and leads reduces the risk of reinfection.

Class IIa

3. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is reasonable in patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy (655, 788, 789). *(Level of Evidence: B)***

Early surgery is associated with a reduction in the rate of embolic complications in patients who present with left-sided IE, severe VHD, and large vegetations (>10 mm). Embolic events are a frequent and life-threatening complication of IE. Embolism is associated with an increased morbidity and mortality in IE and occurs in 20% to 40% of patients with IE. Embolic incidence decreases to 9% to 21% after initiation of antibiotic treatment. Factors associated with a new embolic event are vegetation size >10 mm in length and marked vegetation mobility (especially when associated with the anterior leaflet of the mitral valve). The risk of embolism is highest during the first days after initiation of antibiotic treatment and decreases after 2 weeks.

Patients with PVE who are most likely to benefit from medical therapy without surgery are those with nonstaphylococcal PVE without complications or prosthetic valve dysfunction, as well as those who remain clinically stable and who show clinical improvement on antibiotic treatment. Surgical intervention is especially beneficial in patients with *Staphylococcal* PVE and complicated PVE, of which recurrent embolization is identified as a common type of major complication (>20% of patients in all PVE studies).

Supporting References: (679, 783, 789-791)

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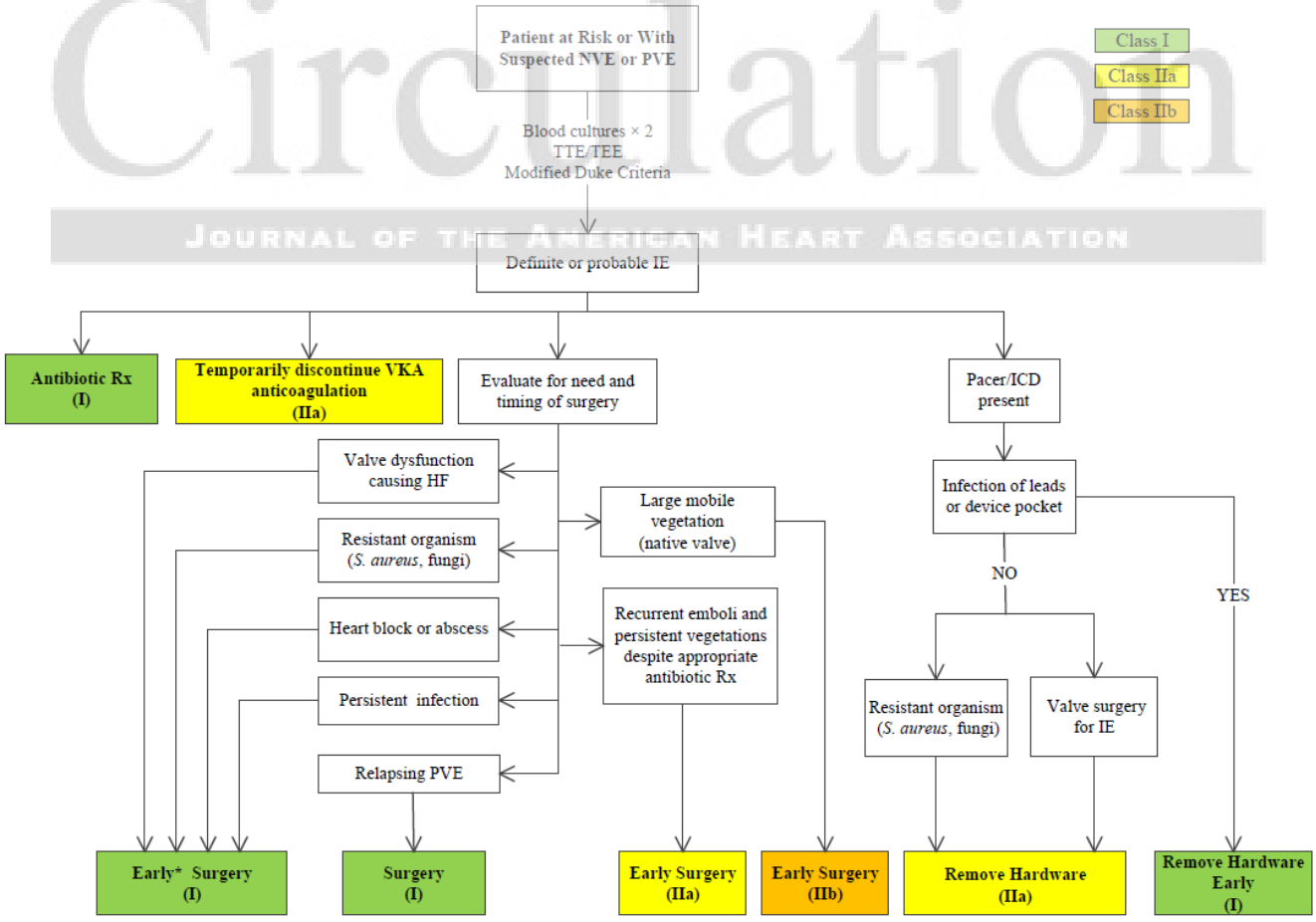
Class IIb

1. **Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered in patients with NVE who exhibit mobile vegetations greater than 10 mm in length (with or without clinical evidence of embolic phenomenon) (655, 788, 789). *(Level of Evidence: B)***

With NVE, large vegetation size is associated with a markedly higher rate of embolic phenomenon. Embolic events are also known to be causally associated with higher rates of mortality in IE. In an RCT of surgical intervention in patients with severe left-sided valve dysfunction and vegetations >10 mm in length (even in the absence of clinically apparent embolic events or HF), there was no significant difference in all-cause mortality at 6 months in the early-surgery versus the conventional-treatment groups (3% and 5%, respectively; p=0.59); however, there was a marked reduction in the number of embolic events, 0% in the early-surgery group compared with 21% in the conventional-treatment group (p=0.005). Additionally, 77% of the conventional group required surgery in the initial hospitalization or during the follow-up phase secondary to HF, paravalvular extension, and heart block.

Supporting References: (652, 789)

Figure 9. Diagnosis and Treatment of IE



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*Early surgery defined as during initial hospitalization before completion of a full therapeutic course of antibiotics.

HF indicates heart failure; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; Rx, therapy; *S. aureus*, *Staphylococcus aureus*; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and VKA, vitamin K antagonist.

13. Pregnancy and VHD

13.1. Native Valve Stenosis: Recommendations

Class I

1. **All patients with suspected valve stenosis should undergo a clinical evaluation and TTE before pregnancy. *(Level of Evidence: C)***

Patients with severe valve stenosis tolerate the hemodynamic changes of pregnancy poorly. The increased cardiac output, increased heart rate, and decreased afterload that occur during pregnancy may all contribute to hemodynamic decompensation in the presence of severe valve stenosis. Thus, it is critical to identify patients who may have suspected valve stenosis before pregnancy, because this finding may have important implications for therapy before conception as well as management during pregnancy and delivery. The most common etiology of AS in women of childbearing age in developed countries is a congenitally abnormal unicuspid or bicuspid valve, which can be associated with an aortopathy. In these patients, it is important to determine the size of the aorta before pregnancy, because those with a dilated aorta may be at increased risk for further dilation during pregnancy. A comprehensive TTE and Doppler echocardiogram should be performed before pregnancy to diagnose the presence of valve stenosis, severity of stenosis, and hemodynamic consequence of the stenosis. *Supporting References:* (792-794)

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Class I

2. **All patients with severe valve stenosis (stages C and D) should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy. *(Level of Evidence: C)***

The management of patients with valve stenosis should ideally begin before conception. A complete assessment of functional capacity, severity of stenosis, and the status of the left ventricle and pulmonary pressures are necessary to determine the risk of pregnancy and delivery in patients with valve stenosis. The risks and benefits of proceeding with pregnancy must be fully discussed with the patient. Interventions before pregnancy, such as valve replacement, valve repair, or percutaneous aortic or mitral balloon dilation should be considered, particularly in those patients with severe stenosis, regardless of symptoms. Drugs with potential harmful effects on the fetus must be identified. If pregnancy is contemplated, arrangements should be made for the patient to be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians who have expertise in managing high-risk cardiac patients. Counseling regarding all these areas should be performed by a cardiologist with expertise in managing patients with VHD during pregnancy.

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Supporting References: (792-794)

Class I

3. **All patients referred for a valve operation before pregnancy should receive prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy about the risks and benefits of all options for operative interventions, including mechanical prosthesis, bioprosthesis, and valve repair.** ***(Level of Evidence: C)***

All prosthetic valve types pose major problems during pregnancy. Patients with mechanical prostheses require continued anticoagulation throughout pregnancy to prevent valve thrombosis and systemic embolism. However, anticoagulation has risks for both the mother and the fetus. Bioprostheses have a limited life span, particularly in the younger patient, and controversy persists as to whether there is acceleration of valve degeneration during pregnancy. Patients of childbearing age who undergo valve surgery should be informed of the maternal and fetal risks of anticoagulation, risk of mechanical valve thrombosis and embolism, and risk of bioprosthetic valve degeneration during pregnancy.

Supporting References: (793, 795)

Class I

4. **Pregnant patients with severe valve stenosis (stages C and D) should be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients during pregnancy.** ***(Level of Evidence: C)***

Patients with severe stenosis are at high risk during pregnancy. The risk increases throughout pregnancy, given the continued hemodynamic changes, including increased intravascular volume, decreased afterload, and increased heart rate. Pulmonary edema, arrhythmias, and even maternal death may occur. The presence of severe valve stenosis is also associated with an increased risk to the fetus. Management of pregnant patients with VHD requires that clinicians have knowledge and experience in caring for these patients. Cardiac diagnostics, hemodynamic monitoring, and prevention of cardiovascular complications require expertise beyond the standard obstetrical scope of practice. Timing and mode of delivery should be discussed jointly and carried out by the Heart Valve Team, with close hemodynamic monitoring during and up to 24 hours after delivery.

Supporting References: (792-794)

13.1.1. Diagnosis and Follow-Up: Recommendation

Class IIa

1. **Exercise testing is reasonable in asymptomatic patients with severe AS (aortic velocity ≥4.0 m per second or mean pressure gradient ≥40 mm Hg, stage C) before pregnancy.** ***(Level of Evidence: C)***

Patients with severe AS have an increased risk of sudden clinical deterioration and even death during pregnancy, particularly in patients who are symptomatic. Exercise testing is reasonable in asymptomatic patients with severe AS before pregnancy to obtain an objective assessment of exercise tolerance. Patients with symptoms

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provoked by exercise testing should be considered symptomatic, especially if the clinical history is equivocal. These patients should be treated for symptomatic severe AS and cautioned against pregnancy or should undergo an intervention such as AVR or percutaneous aortic balloon dilation before conception. Although there are no data on the prognostic value of other findings on exercise testing before pregnancy, high-risk parameters on exercise testing for nonpregnant patients include a limited exercise tolerance or a drop in BP.

Supporting References: (46, 47, 117, 793, 794)

13.1.2. Medical Therapy: Recommendations

Class I

1. **Anticoagulation should be given to pregnant patients with MS and AF unless contraindicated. *(Level of Evidence: C)***

Systemic embolization may occur in up to 10% to 20% of patients with MS, with the highest risk in patients with AF. One third of embolic events occur within the first month of the onset of AF. Anticoagulation will result in a 4- to 15-fold decrease in the incidence of embolic events in nonpregnant patients. Pregnancy is associated with a hypercoagulable state and is expected to further increase the risk of thromboembolic events. Therefore, all patients with MS and AF should receive antithrombotic therapy. Warfarin is the most effective anticoagulant regimen in the second and third trimester. These patients should then be converted to continuous infusion of UFH before planned delivery. The optimal anticoagulation regimen during the first trimester remains controversial and is discussed further in the prosthetic valve and pregnancy section (Section 13.3.2).

Supporting References: (310, 316, 796, 797)

Class IIa

1. **Use of beta blockers as required for rate control is reasonable for pregnant patients with MS in the absence of contraindication if tolerated. *(Level of Evidence: C)***

In patients with MS, the shortening of the diastolic filling period with the increased heart rate of pregnancy results in a rise in LA pressure due to obstruction at the mitral valve level. If stenosis is only mild to moderate, the increase in cardiac output further exacerbates the rise in LA pressure. If MS is severe, the normal rise in cardiac output may be blunted due to the short diastolic filling period across a small mitral orifice. Therapy targeted at reducing heart rate allows a longer diastolic filling period with an improvement in forward cardiac output and reduction in LA pressure. After the first trimester, restricting physical activity helps with heart rate control. In addition, beta-blocker medications are relatively safe for both the mother and the fetus. The use of beta blockers with beta-1 selectivity is preferred because the beta-2 effects on uterine relaxation are avoided. Metoprolol has a lower incidence of fetal growth retardation than atenolol and is the preferred beta blocker for use in pregnancy.

Supporting References: (794, 798-801)

Class IIb

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1. **Use of diuretics may be reasonable for pregnant patients with MS and HF symptoms (stage D). *(Level of Evidence: C)***

Diuretics may be helpful in reducing elevated LA pressure in patients with MS who become symptomatic. However, they should be used with caution due to the potential for reducing placental perfusion.

Supporting Reference: (793)

Class III: Harm

1. **ACE inhibitors and ARBs should not be given to pregnant patients with valve stenosis (802-804). *(Level of Evidence: B)***

ACE inhibitors and ARBs are contraindicated during pregnancy due to fetal toxicity, including renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of the skull, lung hypoplasia, and intrauterine fetal death. If a patient with valve stenosis is taking 1 of these medications for any reason, it should be discontinued or replaced with an alternate medication before conception.

Supporting References: (802-804)

13.1.3. Intervention: Recommendations

Class I

1. **Valve intervention is recommended before pregnancy for symptomatic patients with severe AS (aortic velocity ≥4.0 m per second or mean pressure gradient ≥40 mm Hg, stage D). (*Level of Evidence: C*)**

Patients with severe AS are at high risk for complications during the hemodynamic stress of pregnancy. Early studies demonstrated a very poor outcome for patients with severe AS who become pregnant, with a maternal mortality rate of 17% and fetal and neonatal mortality rate of 32%. Subsequent studies reported better outcomes, but there is still a 3% to 10% risk of complication of HF and up to a 25% risk of arrhythmia. In addition, sudden deterioration and even death may occur, despite meticulous medical care during pregnancy and delivery. Fetal complications, including preterm birth, intrauterine growth retardation, and low birth weight occur in up to 25% of pregnant women with moderate and severe AS. The severity of stenosis and presence of symptoms are predictors of poor outcomes during pregnancy in patients with AS. Valve intervention is recommended for all patients with severe symptomatic AS, regardless of whether or not pregnancy is being contemplated. Women with symptomatic severe AS who wish to become pregnant should have a valve intervention before conception to prevent the possible devastating consequences of progressive or sudden deterioration during pregnancy and delivery. Percutaneous aortic balloon dilation may be considered in patients with noncalcified bicuspid aortic valves, with the understanding that restenosis may occur within several years of the procedure. AVR may also be considered before pregnancy, after a detailed discussion with the patient about the risks and benefits of a bioprosthetic versus a mechanical valve.

Supporting References: (792, 805-810)

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Class I

2. **Valve intervention is recommended before pregnancy for symptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage D). *(Level of Evidence: C)***

Patients with severe MS (mitral valve area ≤1.5 cm^2) are at increased risk for complications during pregnancy. The increased blood volume, heart rate, and cardiac output will more than double the transmitral gradient, significantly increasing LA pressure. Up to 74% of patients with severe MS will have clinical deterioration during pregnancy, manifested primarily by HF symptoms and atrial arrhythmias. The predictors of poor outcome are severity of the stenosis and symptoms before pregnancy. Maternal mortality is uncommon but does occur with severe symptoms and critical MS. Fetal outcome is also dependent on the severity of stenosis and symptoms. The rate of premature delivery is 14% in patients with mild MS and up to 33% in patients with severe MS. If severe symptoms develop, there is a 30% risk of fetal mortality. These complications can be minimized by relief of MS before pregnancy. When valve morphology is favorable, percutaneous mitral balloon commissurotomy is the preferred intervention. In patients with calcified immobile valves and subvalvular fusion, the choice between therapeutic intervention using percutaneous mitral balloon commissurotomy, surgical commissurotomy, or MVR should be made based on institutional experience.

Supporting References: (792, 809-813)

Class I

3. **Percutaneous mitral balloon commissurotomy is recommended before pregnancy for asymptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage C) who have valve morphology favorable for percutaneous mitral balloon commissurotomy. *(Level of Evidence: C)***

Percutaneous mitral balloon commissurotomy can be performed with a high rate of success and low rate of complications in patients with valve anatomy amenable to this procedure. There is a high rate of clinical deterioration that occurs in patients with severe MS during the hemodynamic changes of pregnancy. There is also a high rate of compromised fetal outcome, including growth retardation, prematurity, and low birth weight, which has subsequent consequences on infant morbidity, infant mortality, and patient cardiovascular disease. If valve anatomy is suitable for commissurotomy, percutaneous mitral balloon commissurotomy should be performed in patients with severe MS before conception, even in the absence of symptoms.

Supporting References: (809-814)

Class IIa

1. **Valve intervention is reasonable before pregnancy for asymptomatic patients with severe AS (aortic velocity ≥4.0 m per second or mean pressure gradient ≥40 mm Hg, stage C). *(Level of Evidence: C)***

Most patients with mild-to-moderate AS can tolerate the hemodynamic changes of pregnancy without adverse cardiovascular events. However, patients with severe AS are at an increased risk for complications, with HF developing in 10% to 44% of patients and arrhythmias in up to 25%, even if they were asymptomatic before

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pregnancy. Progressive as well as sudden deterioration may occur in patients with severe AS during pregnancy and delivery. There is also an increased incidence of hypertensive emergencies that occur during pregnancy in patients with severe AS, possibly related to poor placental perfusion. Fetal outcomes are also worse in patients with severe AS. These adverse outcomes can be minimized by relief of AS. Percutaneous aortic balloon dilation may be considered in patients with noncalcified congenital AS, with the understanding that restenosis may occur within several years of the procedure. When anatomy is not suitable for balloon aortic dilation, AVR may be considered before pregnancy, after a detailed discussion with the patient about the risks and benefits of a bioprosthetic versus a mechanical valve.

Supporting References: (805-810)

Class IIa

2. **Percutaneous mitral balloon commissurotomy is reasonable for pregnant patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) with valve morphology favorable for percutaneous mitral balloon commissurotomy who remain symptomatic with NYHA class III to IV HF symptoms despite medical therapy (158, 815-818). *(Level of Evidence: B)***

Patients with severe MS have a high probability of developing progressive symptoms during the hemodynamic changes of pregnancy, particularly during the second and third trimesters. Percutaneous mitral balloon commissurotomy has been performed successfully in pregnant patients with severe MS, primarily in those who have an anatomy that is amenable to this intervention. Although the risk of complications is low, there is still a risk of severe MR requiring urgent MVR. This procedure should be reserved only for those patients who remain symptomatic with NYHA class III to IV HF symptoms after initial therapy with bed rest, beta blockade, and diuretics. Percutaneous mitral balloon commissurotomy should preferably be performed after 20 weeks of gestation, the period safest for the fetus. Percutaneous mitral balloon commissurotomy during pregnancy should only be performed by experienced operators who have a demonstrated low complication rate, minimizing radiation dose to the mother and fetus. The procedure should also be done with back-up cardiac surgery, anesthesiology, and high-risk obstetrics services in place.

Supporting References: (158, 815-818)

Class IIa

3. **Valve intervention is reasonable for pregnant patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) and valve morphology not favorable for percutaneous mitral balloon commissurotomy only if there are refractory NYHA class IV HF symptoms. *(Level of Evidence: C)***

Patients with severe MS and unfavorable valve morphology (i.e., severe leaflet calcification, leaflet thickening, immobility, subvalvular fusion, and commissural calcification) are at high risk for percutaneous mitral balloon commissurotomy. In these patients, the percutaneous approach may be complicated by severe MR requiring emergency MVR. Although percutaneous balloon mitral commissurotomy remains an option, MVR under controlled surgical conditions is the safest approach in this subgroup of patients. However, valve operation during pregnancy is high risk, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate.

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Surgery for MS during pregnancy should be reserved for those with refractory NYHA class IV HF symptoms that are not responsive to medical therapy. The operation needs to be carefully planned with a Heart Valve Team of cardiologists, cardiovascular anesthesiologists, surgeons, and obstetricians specializing in high-risk obstetrics to determine optimal timing and sequence of therapies. High pump flows and normothermic perfusion should be used to protect the fetus during cardiopulmonary bypass, with the shortest pump time possible. Continued monitoring of the fetus should be performed. There is no ideal time during pregnancy to perform open heart surgery, so timing is based on the combination of the clinical status of the mother and the fetus. The period between the 20th and 28th weeks of pregnancy appears to be safest for the fetus in terms of risk of malformation and premature delivery. If the mother can carry the fetus to full maturity, a combined cesarean section followed by cardiac surgery can be planned.

Supporting References: (816, 819-822)

Class IIa

4. **Valve intervention is reasonable for pregnant patients with severe AS (mean pressure gradient ≥40 mm Hg, stage D) only if there is hemodynamic deterioration or NYHA class III to IV HF symptoms (805, 823-828).** ***(Level of Evidence: B)***

Patients with severe AS may develop progressive HF or sudden hemodynamic deterioration during the hemodynamic stress of pregnancy. Medical therapy is of limited efficacy, as the AS is a fixed mechanical obstruction. Both open heart surgery and percutaneous aortic balloon dilation are high-risk procedures during pregnancy for both the mother and the fetus and should only be performed if there is hemodynamic deterioration or severe NYHA class III to IV HF symptoms. The type of intervention (AVR or percutaneous aortic balloon dilation) will be dependent on the expertise of the center but should always be performed in a center with a multidisciplinary group of cardiologists, interventionalists, cardiac anesthesiologists, and obstetricians specializing in high-risk obstetrics.

There have been reports of successful percutaneous aortic balloon dilation during pregnancy. This procedure has better results in patients with the noncalcified bicuspid aortic valve but may result in severe AR due to a tear in an aortic valve cusp. Limited fluoroscopy time with appropriate lead shielding of the fetus is necessary. Intervention is preferable after 20 weeks of gestation because it is safer for the fetus. Percutaneous aortic balloon dilation should only be performed by highly experienced operators in centers with a competent team of cardiologists and cardiovascular anesthesiologists, with back-up cardiac surgery and high-risk obstetrics services in place.

AVR may also be considered. High pump flows and normothermic perfusion should be used to protect the fetus during cardiopulmonary bypass, with the shortest pump time possible. Continued monitoring of the fetus should be performed. There is no ideal time during pregnancy to perform open heart surgery, so timing is based on the combination of the clinical status of the mother and the fetus. The period between the 20th and 28th weeks of pregnancy appears to be safest for the fetus in terms of risk of malformation and premature

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delivery. If the mother can carry the fetus to full maturity, a combined cesarean section followed by cardiac operation can be planned.

Percutaneous aortic balloon dilation and AVR procedures need to be carefully planned with a Heart Valve Team of cardiologists, cardiovascular anesthesiologists, surgeons, and obstetricians specializing in high-risk obstetrics to determine optimal timing and sequence of therapies.

Supporting References: (805, 816, 819-828)

Class III: Harm

1. **Valve operation should not be performed in pregnant patients with valve stenosis in the absence of severe HF symptoms. *(Level of Evidence: C)***

Valve surgery during pregnancy is high risk, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate reported. It should be reserved only for patients with severe, intractable symptoms unresponsive to bed rest and medical therapy.

Supporting References: (816, 819-822)

13.2. Native Valve Regurgitation

13.2.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **All patients with suspected valve regurgitation should undergo a clinical evaluation and TTE before pregnancy. *(Level of Evidence: C)***

Patients with valve regurgitation tolerate pregnancy better than patients with valve stenosis do because the decrease in afterload that occurs throughout pregnancy allows an appropriate increase in cardiac output without a rise in ventricular filling pressures. However, patients with severe regurgitation who are already symptom limited or have a reduced LVEF or pulmonary hypertension may develop HF symptoms because of the volume load of pregnancy. Clinical and TTE evaluation before pregnancy allow determination of the cause of regurgitation, quantitation of regurgitant severity, measurement of LVEF, and estimation of pulmonary pressures so that patients at high risk can be identified.

Supporting References: (792-794, 810, 829-834)

Class I

2. **All patients with severe valve regurgitation (stages C and D) should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy. *(Level of Evidence: C)***

The management of patients with valve regurgitation should ideally begin before conception. A complete assessment of functional capacity, severity of regurgitation, pulmonary pressures, and LV size and function are necessary to determine the risk of pregnancy and delivery in patients with valve regurgitation. The risks and benefits of proceeding with pregnancy must be fully discussed with the patient. Interventions before pregnancy

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may be considered in the patient with severe regurgitation who is at high risk for developing HF during pregnancy, particularly if the valve can be repaired instead of replaced. Drugs with potential harmful effects on the fetus must be identified. If pregnancy is contemplated, arrangements should be made for the patient to be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in managing high-risk cardiac patients. Counseling regarding all these areas should be performed by a cardiologist with expertise in managing patients with VHD during pregnancy.

Supporting References: (792-794, 810, 834)

Class I

3. **All patients referred for a valve operation before pregnancy should receive prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy regarding the risks and benefits of all options for operative interventions, including mechanical prosthesis, bioprosthesis, and valve repair. *(Level of Evidence: C)***

When intervention is indicated, valve repair is preferred for the treatment of valve regurgitation in women of childbearing age. However, not all valves can be adequately repaired, and the decision to proceed with implantation of a prosthetic valve is sometimes made at the time of operation. All prosthetic valve types pose major problems during pregnancy. Mechanical prostheses require continued anticoagulation throughout pregnancy, with risks to both the mother and the fetus. Bioprostheses have a limited life span, particularly in the younger patient, and controversy persists as to whether there is acceleration of valve degeneration during pregnancy. All patients of childbearing age being considered for a valve operation should receive prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy to discuss the risks and benefits of available treatment options.

Supporting References: (793, 795, 810, 834)

Class I

4. **Pregnant patients with severe regurgitation (stages C and D) should be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in managing high-risk cardiac patients. *(Level of Evidence: C)***

Patients with severe regurgitation may be at high risk during pregnancy. The risk increases throughout pregnancy, given the continued physiological hemodynamic changes, including increased volume, decreased afterload, and increased heart rate. Pulmonary edema, arrhythmias, and even maternal death may occur. The presence of severe valve regurgitation is also associated with an increased risk to the fetus. Timing and mode of delivery should be discussed and carried out by the Heart Valve Team, with close hemodynamic monitoring during and up to 24 hours after delivery. Management at a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians who have expertise in the care of high-risk cardiac patients will ensure optimal maternal and fetal outcomes in women with severe valve regurgitation.

Supporting References: (792-794, 810, 834)

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Class IIa

1. **Exercise testing is reasonable in asymptomatic patients with severe valve regurgitation (stage C) before pregnancy. *(Level of Evidence: C)***

Asymptomatic patients with severe valve regurgitation usually tolerate the hemodynamic changes of pregnancy, unless there is concurrent ventricular systolic dysfunction or pulmonary hypertension. Exercise testing may identify apparently asymptomatic patients at higher risk of complications during pregnancy. Exercise parameters suggesting a higher risk include limited exercise tolerance, exercise-induced pulmonary hypertension, or abnormal symptoms. Patients with symptoms provoked by exercise testing should be considered symptomatic.
Supporting References: (793, 810, 834)

13.2.2. Medical Therapy: Recommendation

Class III: Harm

1. **ACE inhibitors and ARBs should not be given to pregnant patients with valve regurgitation (802-804). *(Level of Evidence: B)***

ACE inhibitors and ARBs are contraindicated during pregnancy due to fetal toxicity, including renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of the skull, lung hypoplasia, and intrauterine fetal death. If a patient with valvular regurgitation is taking 1 of these medications for any reason, it should be discontinued or replaced with an alternate medication before conception.
Supporting References: (802-804)

13.2.3. Intervention: Recommendations

Class I

1. **Valve repair or replacement is recommended before pregnancy for symptomatic women with severe valve regurgitation (stage D). *(Level of Evidence: C)***

Symptomatic women with severe valve regurgitation are at high risk for developing HF during pregnancy. All patients with symptomatic severe valve regurgitation should undergo surgery to repair or replace the valve, regardless of whether they wish to become pregnant. The operation will improve long-term outcomes and prevent progressive ventricular dysfunction from the long-standing volume overload. Although the ideal operation would be valve repair, not all valves can be successfully repaired. Potential problems associated with the different types of prosthetic valves during pregnancy must be discussed in detail with all women before operation.
Supporting References: (793, 810, 834)

Class IIa

1. **Valve operation for pregnant patients with severe valve regurgitation is reasonable only if there are refractory NYHA class IV HF symptoms (stage D). *(Level of Evidence: C)***

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Valve operation during pregnancy is high risk for both the mother and the fetus, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate reported. Thus, it should be reserved for the very rare patient with severe valve regurgitation who has severe refractory HF symptoms. The operation needs to be carefully planned with the multidisciplinary Heart Valve Team of cardiologists, cardiovascular anesthesiologists, surgeons, and high-risk obstetricians to determine optimal timing and sequence of therapies. High pump flows and normothermic perfusion should be used to protect the fetus during cardiopulmonary bypass, with the shortest pump time possible. Continuous monitoring of the fetus should be performed. There is no ideal time during pregnancy to perform open heart surgery, so timing is based on the combination of the clinical status of the mother and the fetus. The period between the 20th and 28th weeks of pregnancy appears to be safest for the fetus in terms of risk of malformation and premature delivery. If the mother can carry the fetus to full maturity, a combined cesarean section followed by cardiac operation can be planned.

Supporting References: (819-822)

Class IIb

1. **Valve repair before pregnancy may be considered in the asymptomatic patient with severe MR (stage C) and a valve suitable for valve repair, but only after detailed discussion with the patient about the risks and benefits of the operation and its outcome on future pregnancies. *(Level of Evidence: C)***

The threshold for valve operation for valve regurgitation should be higher in the asymptomatic patient who wants to become pregnant as opposed to conventional criteria in patients who are not likely to become pregnant. Although a successful mitral valve repair will result in a low-risk pregnancy and delivery, not all valves can be successfully repaired with complete certainty. If surgery is undertaken and valve repair is unsuccessful, the implantation of a mitral valve prosthesis increases the risks during pregnancy, regardless of whether a mechanical or bioprosthetic valve is used. Most patients with asymptomatic severe MR tolerate pregnancy, and there is no evidence for acceleration of LV dysfunction during pregnancy. Thus, it may be prudent to manage these patients medically rather than recommending valve surgery before pregnancy. In patients with MR who are at higher risk for the development of HF during pregnancy, including those with depressed LV systolic function or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg), the decision to operate before pregnancy should take into consideration the mitral valve morphology, chance of successful repair in the institution, estimated surgical risk, and issues related to possible MVR. This may require referral to a Heart Valve Center of Excellence if the expected rate of a successful and durable valve repair at the institution does not exceed 95%.

Supporting References: (793, 810, 834)

Class III: Harm

1. **Valve operations should not be performed in pregnant patients with valve regurgitation in the absence of severe intractable HF symptoms. (*Level of Evidence: C*)**

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Valve surgery during pregnancy is high risk, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate reported. It should be reserved only for patients with severe, intractable symptoms unresponsive to bed rest and medical therapy.

Supporting References: (819-822)

13.3. Prosthetic Valves in Pregnancy

13.3.1. Diagnosis and Follow-Up: Recommendations

Class I

1. **All patients with a prosthetic valve should undergo a clinical evaluation and baseline TTE before pregnancy. *(Level of Evidence: C)***

Major complications can occur during pregnancy in patients with prosthetic valves. The increased hemodynamic burden of pregnancy can lead to HF if there is prosthetic valve thrombosis, stenosis, regurgitation, or patient-prosthesis mismatch. Clinical evaluation and baseline TTE allow determination of valve function and hemodynamics under normal loading conditions and help identify valve dysfunction that might require treatment before pregnancy. In addition, there is an increased risk of valve thrombosis in patients with a mechanical prosthesis due to the hypercoagulable state of pregnancy. The baseline TTE serves as the reference standard for the patient if valve thrombosis is suspected during pregnancy.

Supporting References: (793, 795)

Class I

2. **All patients with a prosthetic valve should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy. *(Level of Evidence: C)***

The management of the pregnant patient with a prosthetic valve may significantly differ from that of the patient who is not pregnant, specifically in relation to antithrombotic therapy. There is a much higher risk of valve thrombosis for patients with a mechanical prosthesis due to the hypercoagulable state of pregnancy. Certain drugs are contraindicated during pregnancy. Prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy should be performed to determine the risk of pregnancy, discuss potential complications, and outline an approach for anticoagulation at the time of conception.

Supporting References: (793, 795)

Class I

3. **TTE should be performed in all pregnant patients with a prosthetic valve if not done before pregnancy. *(Level of Evidence: C)***

Although it is preferable to perform a baseline echocardiogram before pregnancy in women with prosthetic heart valves, if a baseline study is not available during the time the patient has been clinically stable, TTE during pregnancy still provides evaluation of prosthetic valve function, as well as ventricular function and pulmonary

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pressures. Due to an increase in cardiac output that occurs during pregnancy, the mean pressure gradient across all prostheses will increase throughout the first and second trimesters and remain elevated in the third trimester. Other hemodynamic parameters such as diastolic half-time (for a mitral prosthesis) and dimensionless index (the ratio of the LV outflow time velocity divided by the peak aortic valve velocity for an aortic prosthesis) must be used to determine the function of the prosthesis.

Supporting References: (793, 795)

Class I

4. **Repeat TTE should be performed in all pregnant patients with a prosthetic valve who develop symptoms. *(Level of Evidence: C)***

If there are changes in clinical status with either the onset of symptoms of dyspnea or change in the clinical examination, a repeat echocardiogram is indicated to look for changes in ventricular function and in the hemodynamics of the prosthetic valve. Bioprosthetic valves are at risk for tissue degeneration; bioprosthetic valve stenosis typically develops slowly, but bioprosthetic regurgitation may be acute due to a leaflet tear adjacent to an area of calcification. Mechanical valves are prone to acute stenosis or regurgitation during pregnancy due to valve thrombosis limiting disc opening or closure. TTE should be performed initially because both aortic and mitral transvalvular flows can be recorded from this approach. However, TEE is needed if prosthetic MR is suspected. Although radiation exposure should be minimized, fluoroscopy of mechanical valves may be helpful in evaluating disc motion.

Supporting References: (793, 795)

Class I

5. **TEE should be performed in all pregnant patients with a mechanical prosthetic valve who have prosthetic valve obstruction or experience an embolic event. *(Level of Evidence: C)***

If thrombotic obstruction is suspected or if an embolic event occurs in a pregnant patient with a mechanical prosthesis, TEE is indicated to look at valve function and disc motion and to determine the thrombus burden. Subsequent therapeutic decisions will depend on the clinical state of the patient, gestational age of the child, degree of valve dysfunction, and thrombus burden. TEE is especially important for detection of prosthetic mitral valve dysfunction, and an apparently normal transthoracic study should not dissuade clinicians from proceeding with TEE. With a prosthetic aortic valve, both TTE and TEE are needed for a complete examination. Chest CT imaging can also diagnose prosthetic valve thrombosis and limitations of mechanical valve motion but should be avoided during pregnancy due to radiation exposure.

Supporting References: (605, 793, 795, 835-837)

Class I

6. **Pregnant patients with a mechanical prosthesis should be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients. *(Level of Evidence: C)***

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Women with mechanical valves are at high risk of devastating complications during pregnancy. There is an increased risk for thrombosis of mechanical valves due to the hypercoagulable state of pregnancy, particularly those with a prosthetic valve in the mitral position. Anticoagulation regimens to prevent valve thrombosis require in-depth knowledge of the risks and benefits of each approach. Valve thrombosis may result in acute, severe HF and/or embolic events, with a high-resultant maternal and fetal mortality. The occurrence of valve thrombosis during pregnancy constitutes a medical and sometimes surgical emergency. Integrated care by a Heart Valve Team of cardiologists, surgeons, anesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients is needed.

Supporting References: (793, 795)

13.3.2. Medical Therapy: Recommendations

See Figure 10 for anticoagulation of pregnant patients with mechanical valves.

Class I

1. **Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis (838, 839).** ***(Level of Evidence: B)***

There is a high risk of valve thrombosis in patients with mechanical prostheses who are pregnant due to the hypercoagulable state that occurs during pregnancy. All anticoagulant regimens carry an increased risk to the fetus, with fetal abnormalities, an increased risk of miscarriage, and hemorrhagic complications, including retroplacental bleeding, leading to premature birth and fetal death. However, without any anticoagulation, maternal mortality is high (up to 5%), and there is a high risk of thromboembolic events (up to 24%) and valve thrombosis. Because of the physiological effects of pregnancy, there are constantly changing requirements for antithrombotic regimens. Effective anticoagulation with frequent monitoring of its systemic effect is critical throughout the pregnancy.

Supporting References: (838, 839)

See Online Data Supplement 25 for more information on pregnancy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

2. **Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimesters (840-845).** ***(Level of Evidence: B)***

Warfarin is the most effective anticoagulant for preventing maternal thromboembolic events during pregnancy. Although warfarin has potential fetal teratogenic effects in the first trimester, there is little teratogenic effect in the second and third trimesters. Use of UFH throughout pregnancy has the highest risk of thromboembolic events and maternal death in patients with a mechanical prosthesis, with reported instances of massive thrombosis of prosthetic valves. Although there are no RCTs comparing the different antithrombotic regimens, the risk of thromboembolic events using warfarin throughout pregnancy is <4%, compared with 33% with the

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use of UFH throughout pregnancy. Use of UFH throughout pregnancy is also associated with maternal complications of thrombocytopenia and osteoporosis. LMWH given at a fixed dose has resulted in fatal valve thrombosis. When monitored with anti-Xa levels, LMWH has a lower rate of valve thrombosis compared with UFH. Even with meticulous monitoring of anti-Xa levels, there have been cases of valve thrombosis with LMWH used throughout pregnancy. There is no ideal anticoagulant regimen for pregnant women with mechanical valves. However, during the second and third trimesters of pregnancy, the benefits of warfarin for the mother appear to outweigh the slightly increased risk to the fetus.

Supporting References: (838, 840-847)

See Online Data Supplements 25 and 26 for more information on pregnancy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class I

3. **Discontinuation of warfarin with initiation of intravenous UFH (with an activated partial thromboplastin time [aPTT] >2 times control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis. *(Level of Evidence: C)***

Warfarin crosses the placental barrier and results in anticoagulation of the fetus as well as the mother. There is a higher risk of intracranial hemorrhage for the fetus if the mother is fully anticoagulated during vaginal delivery. It is recommended that the mother be hospitalized before planned delivery with discontinuation of warfarin and initiation of intravenous continuous infusion of UFH to keep aPTT >2 times control levels. Then heparin is stopped just before delivery. Patients with mechanical prostheses are at increased risk for premature labor, so careful planning with a Heart Valve Team of cardiologists, anesthesiologists, and obstetricians is required before anticipated delivery. Alternative approaches to delivery include elective cesarean section after a shorter cessation of warfarin.

Supporting References: (848, 849)

Class I

4. **Low-dose aspirin (75 mg to 100 mg) once per day is recommended for pregnant patients in the second and third trimesters with either a mechanical prosthesis or bioprosthesis. *(Level of Evidence: C)***

Although there are no data regarding the addition of aspirin to anticoagulation in pregnant patients with prosthetic valves, the addition of aspirin is effective in lowering the thromboembolic risk in nonpregnant patients. Aspirin is safe in the second and third trimesters of pregnancy from the obstetrical standpoint.

Supporting References: (567, 568, 850)

Class IIa

1. **Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg per day or less after full discussion with the patient about risks and benefits (838, 839, 844, 845, 848, 851). *(Level of Evidence: B)***

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The optimal anticoagulant used during the first trimester in pregnant patients with mechanical prosthetic valves remains controversial. Oral anticoagulation with warfarin is the safest regimen for the mother, but there is an increased risk of embryopathy. Anticoagulation with UFH or LMWH has been recommended to avoid the risk of embryopathy, but it is not as effective as warfarin in preventing thromboembolic events. The risk of embryopathy is dose dependent, with a low risk (<3%) if the dose of warfarin is ≤5 mg per day. The risk of abortion and fetal loss are increased with any anticoagulant regimen but may be similar in women exposed to oral anticoagulants versus heparin in the first trimester, especially at low doses of warfarin. Continuation of warfarin during the first trimester is reasonable after a full discussion with the patient and family about the risks and benefits when a therapeutic INR can be maintained with a daily warfarin dose of ≤5 mg.
Supporting References: (838, 839, 844, 845, 848, 851-854)

See Online Data Supplements 25 and 26 for more information on pregnancy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIa

2. **Dose-adjusted LMWH at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg per day to achieve a therapeutic INR (840-843, 855, 856). *(Level of Evidence: B)***

In patients whose dosage of warfarin is >5 mg per day, the risk of embryopathy is >8% (compared with <3% with a warfarin dosage of ≤5 mg per day). It is reasonable to consider heparin anticoagulation instead of warfarin during the first trimester of pregnancy, because heparin does not cross the placental barrier and is not associated with fetal embryopathy. LMWH may be a better alternative than UFH with potential advantages of better subcutaneous absorption and bioavailability, longer half-life, and a more predictable anticoagulation response. Anti-Xa levels should be monitored because dosage requirements may increase by as much as 50% over the course of pregnancy. The target anti-Xa level should be 0.8 U/mL to 1.2 U/mL, measured 4 to 6 hours after injection. With use of this meticulous dosing regimen, the incidence of valve thrombosis is lower than with UFH, but there are still reports of valve thrombosis, even with the newer-generation mechanical prostheses. The data for use of LMWH in pregnancy are incomplete, with unresolved questions to be addressed, including optimal anti-Xa levels, use of peak and trough levels, optimal timing of dosage, and compliance issues with dosing 2 times a day and sometimes 3 times a day. If the patient chooses not to be on an oral anticoagulant in the first trimester, dose-adjusted LMWH is a reasonable choice of anticoagulation.
Supporting References: (840-843, 846, 855-857)

See Online Data Supplements 25 and 26 for more information on pregnancy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIa

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3. **Dose-adjusted continuous intravenous UFH (with an aPTT at least 2 times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg per day to achieve a therapeutic INR (838, 839, 848). *(Level of Evidence: B)***

If the decision is made to use UFH during the first trimester of pregnancy, it is reasonable that the patient receive a continuous infusion of heparin, with carefully monitoring of aPTT and a goal of at least >2 times control. Prior studies have shown that the use of subcutaneous UFH is associated with a high incidence of valve thrombosis, especially with older-generation valve prostheses. Disadvantages of intravenous UFH include an increased risk of serious infection and a risk of osteoporosis.

Supporting References: (838, 839, 848)

See Online Data Supplements 25 and 26 for more information on pregnancy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIb

1. **Dose-adjusted LMWH at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg per day or less to achieve a therapeutic INR (840-843, 855-857). *(Level of Evidence: B)***

The choice of type of anticoagulation during the first trimester requires a detailed discussion with the patient about the risks and benefits of the different regimens. The use of warfarin during the first trimester is associated with an increased risk of warfarin embryopathy, but the risk is low (<3%) if the daily dose of warfarin is ≤5 mg. The use of heparin will avoid the risk of embryopathy but is associated with an increased risk of valve thrombosis and embolic events. If the patient decides not to continue warfarin during the first trimester, after a full discussion of the risks and benefits of the different regimens, dose-adjusted LMWH appears to be the safest choice in terms of prevention of thromboembolic events. However, this does require meticulous monitoring of anti-Xa levels, as dosing requirements change throughout pregnancy. The recommended target is an anti-Xa level of 0.8 U/mL to 1.2 U/mL at 4 to 6 hours postdose, given at least 2 times a day.

Supporting References: (840-843, 846, 855-857)

See Online Data Supplements 25 and 26 for more information on pregnancy
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class IIb

2. **Dose-adjusted continuous infusion of UFH (with aPTT at least 2 times control) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg per day or less to achieve a therapeutic INR (838, 839, 848). *(Level of Evidence: B)***

If the patient on a dose of warfarin ≤5 mg per day decides not to continue warfarin during the first trimester, after a full discussion of the risks and benefits of the different regimens, dose-adjusted LMWH appears to be the

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safest choice in terms of prevention of thromboembolic events. If the decision is made to use UFH during the first trimester of pregnancy, it is reasonable that the patient receive a continuous infusion of heparin, with careful monitoring of aPTT with a goal of at least >2 times control. Subcutaneous UFH is associated with a high incidence of valve thrombosis, especially with the older-generation valve prostheses. Intravenous UFH is associated with an increased risk of infection from the prolonged use of intravenous catheters and a risk of osteoporosis.

Supporting References: (838, 839, 848)

See Online Data Supplements 25 and 26 for more information on pregnancy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

Class III: Harm

1. **LMWH should not be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4 to 6 hours after administration (841, 842, 847, 855, 856). *(Level of Evidence: B)***

Initial studies using subcutaneous LMWH at a fixed dose without monitoring of anti-Xa levels in pregnant patients with a mechanical prosthesis were associated with a high risk of valve thrombosis, leading to maternal deaths. Since the requirements of LMWH increase throughout pregnancy, there should be meticulous monitoring of anti-Xa levels, 4 to 6 hours after administration if dose-adjusted administration of LMWH is to be used.

Supporting References: (841, 842, 847, 855, 856)

Figure 10. Anticoagulation of Pregnant Patients With Mechanical Valves

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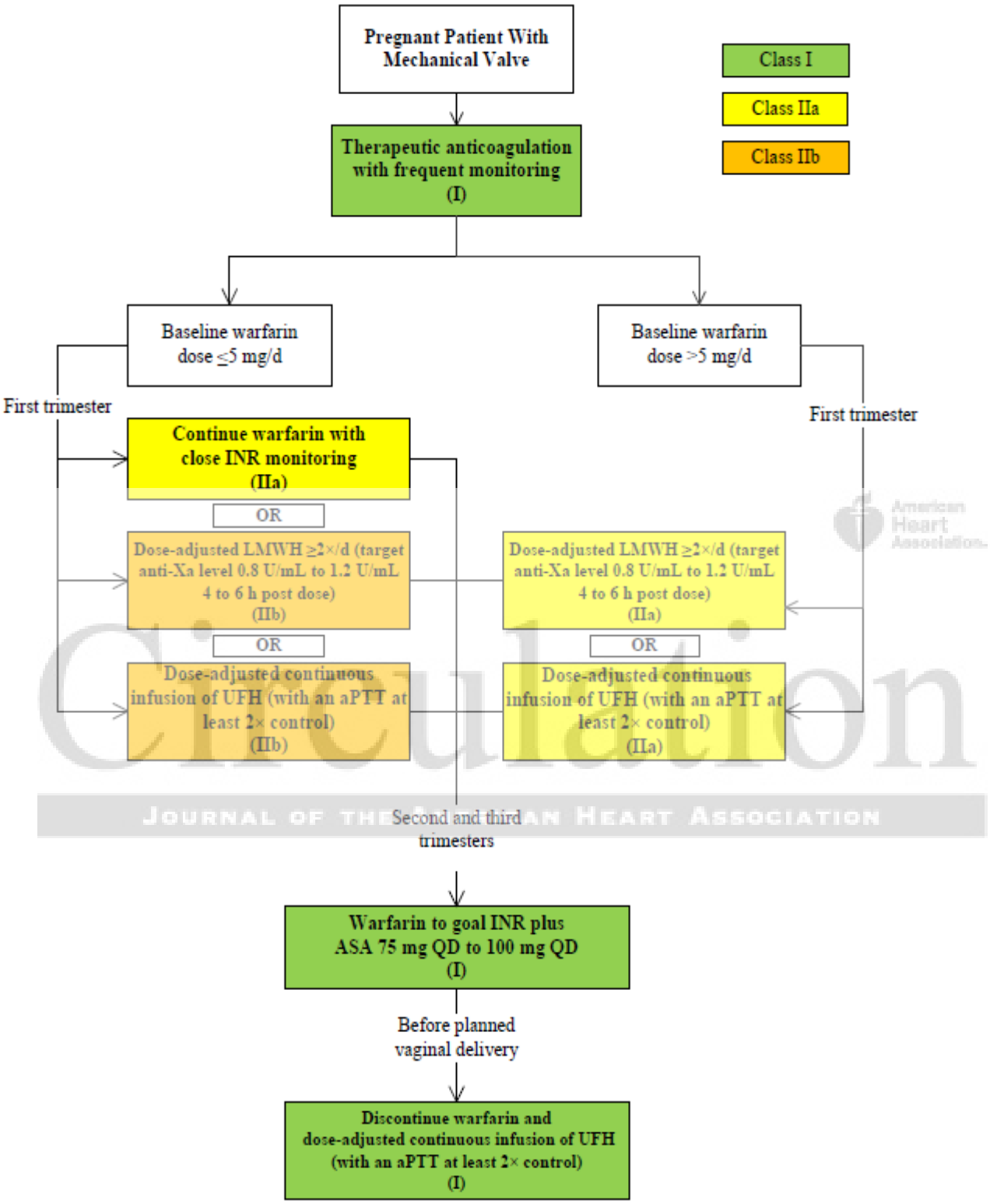

aPTT indicates activated partial thromboplastin time; ASA, aspirin; INR, international normalized ratio; LMWH, low-molecular-weight heparin; QD, once daily; and UFH, unfractionated heparin.

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14. Surgical Considerations

14.1. Evaluation of Coronary Anatomy: Recommendations

See Figure 11 for evaluation and management of CAD in patients undergoing valve surgery.

Screening coronary angiography to assess associated CAD should be considered in selected patients before cardiac surgery or transcatheter intervention for VHD. Invasive selective coronary angiography remains the gold standard. Fractional flow reserve may better delineate the physiological significance of a coronary lesion, but there are no outcome data for its utility in patients undergoing valve surgery. Due to its high negative predictive value, coronary CT angiography to exclude CAD may be an option in patients with low or intermediate pretest probability of CAD. If significant epicardial CAD is present, concomitant CABG should be considered at the time of valve surgery. The presence of severe CAD may also be helpful in determining whether a surgical or transcatheter approach is optimal in patients with AS.

Class I

1. **Coronary angiography is indicated before valve intervention in patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men age >40 years and postmenopausal women).** ***(Level of Evidence: C)***

Knowledge of the coronary anatomy contributes to risk stratification and determines if concomitant coronary revascularization is indicated. Coronary angiography can be avoided in young patients (men <40 years of age and premenopausal women) with no atherosclerotic risk factors and in patients in whom the risks outweigh the benefits, such as in patients with acute aortic dissection, large aortic valve vegetation, or occlusive prosthetic thrombosis.

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Supporting References: (858-871)

Class I

2. **Coronary angiography should be performed as part of the evaluation of patients with chronic severe secondary MR.** ***(Level of Evidence: C)***

In patients with chronic secondary MR, the valve leaflets and chordae are structurally normal and the MR results from the geometrical distortion of the mitral apparatus. This is due to multiple factors that can cause displacement of the papillary muscles, tethering of the leaflets, annular dilation, and decreased closing forces from reduced contractility. Because CAD and accompanying myocardial ischemia may contribute to chronic secondary MR, the assessment of coronary anatomy status is necessary to complete the diagnosis and allow evaluation of revascularization options.

Supporting References: (309, 872-875)

Class IIa

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1. **Surgery without coronary angiography is reasonable for patients having emergency valve surgery for acute valve regurgitation, disease of the aortic sinuses or ascending aorta, or IE. *(Level of Evidence: C)***

Assessment of coronary artery anatomy is rarely required in patients undergoing emergency valve surgery for acute AR, aortic dissection, or IE with hemodynamic instability.

Supporting References: (189, 876-879)

Class IIa

2. **CT coronary angiography is reasonable to exclude the presence of significant obstructive CAD in selected patients with a low/intermediate pretest probability of CAD. A positive coronary CT angiogram (the presence of any epicardial CAD) is confirmed with invasive coronary angiography (880-886). *(Level of Evidence: B)***

In select patients who are at low-to-intermediate pretest probability of CAD and who are being considered for angiography before valve surgery, coronary CT angiography is a reasonable alternative. This does not include patients who have active symptoms of angina, those with documented ischemia, or those with a prior history of CAD, all of whom should have selective coronary angiography. Several small studies have reported high diagnostic accuracy of coronary CT angiography in select patients with VHD. One study of 98 consecutive patients with significant VHD and guideline-based indications for coronary angiography underwent CT coronary angiography if their coronary calcium score was <1,000. Invasive coronary angiography was performed in patients with at least 1 of the following: >50% stenosis, calcium artifacts, or motion artifacts. CT coronary angiography excluded the presence of significant CAD in 80.6% of patients without the need for invasive angiography. Conventional coronary angiography was required in 19.4% of patients because of >50% stenosis in 13.3%, calcium artifact in 2%, and motion artifact in 1%. In another study of 70 patients, 31 had AS (44%), 24 had MR (34%), 9 had AR (13%), and the remainder had other valvular or congenital lesions. On a per-patient basis, sensitivity was 100% (18 of 18 patients with significant CAD) and specificity was 92% (48 of 52 patients without significant CAD). The corresponding negative likelihood ratio is 0.01, which means a negative test would be associated with a very low posttest probability of disease for patients with low and intermediate pretest probabilities. Assuming that all patients would have previously been referred for invasive angiography, coronary CT angiography allowed the 48 patients (69%) in the study cohort with negative CT findings to avoid this procedure. However, a positive coronary CT angiogram, defined as the presence of epicardial CAD, requires confirmation with invasive coronary angiography to establish the need for and extent of CABG. The risk of radiation exposure and renal failure due to the contrast injection should be taken into consideration.

Supporting References: (880-887)

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14.2. Concomitant Procedures

14.2.1. Intervention for CAD: Recommendation

In patients undergoing AVR who also have significant CAD, the combination of CABG and AVR reduces the rates of perioperative MI, perioperative mortality, late mortality, and morbidity when compared with patients not undergoing simultaneous CABG, even though the combined operation carries a small but real increased risk of mortality. The alternative in some patients of a hybrid approach of surgical valve replacement and PCI is attractive, but there are no data at this time to support this approach.

Supporting References: (859, 888)

Class IIa

1. **CABG or PCI is reasonable in patients undergoing valve repair or replacement with significant CAD (≥70% reduction in luminal diameter in major coronary arteries or ≥50% reduction in luminal diameter in the left main coronary artery). *(Level of Evidence: C)***

Several studies have reported the outcomes of patients undergoing combined CABG and valve operation. Although combined myocardial revascularization and valve operation increases cross-clamp time and has the potential to increase perioperative MI and early postoperative mortality compared with patients without CAD undergoing isolated valve surgery, in several series, combined CABG had little or no adverse effect on operative mortality. Moreover, combined CABG and valve operation reduces the rates of perioperative MI, operative mortality and late mortality, and morbidity compared with patients with significant CAD who do not undergo revascularization at the time of valve operation. Incomplete revascularization is associated with greater postoperative LV systolic dysfunction and reduced survival rates after surgery compared with patients who receive complete revascularization. For more than a decade, improved myocardial preservation techniques have been associated with reduced overall operative mortality, and it has become standard practice to bypass all significant coronary artery stenoses when possible in patients undergoing valve surgery. In patients with a significant stenosis of the left anterior descending artery, a left internal thoracic artery graft should be used if possible. No RCTs fully support the use of concomitant coronary revascularization in all patients with asymptomatic CAD undergoing valve operation.

Supporting References: (889-895)

Figure 11. Evaluation and Management of CAD in Patients Undergoing Valve Surgery

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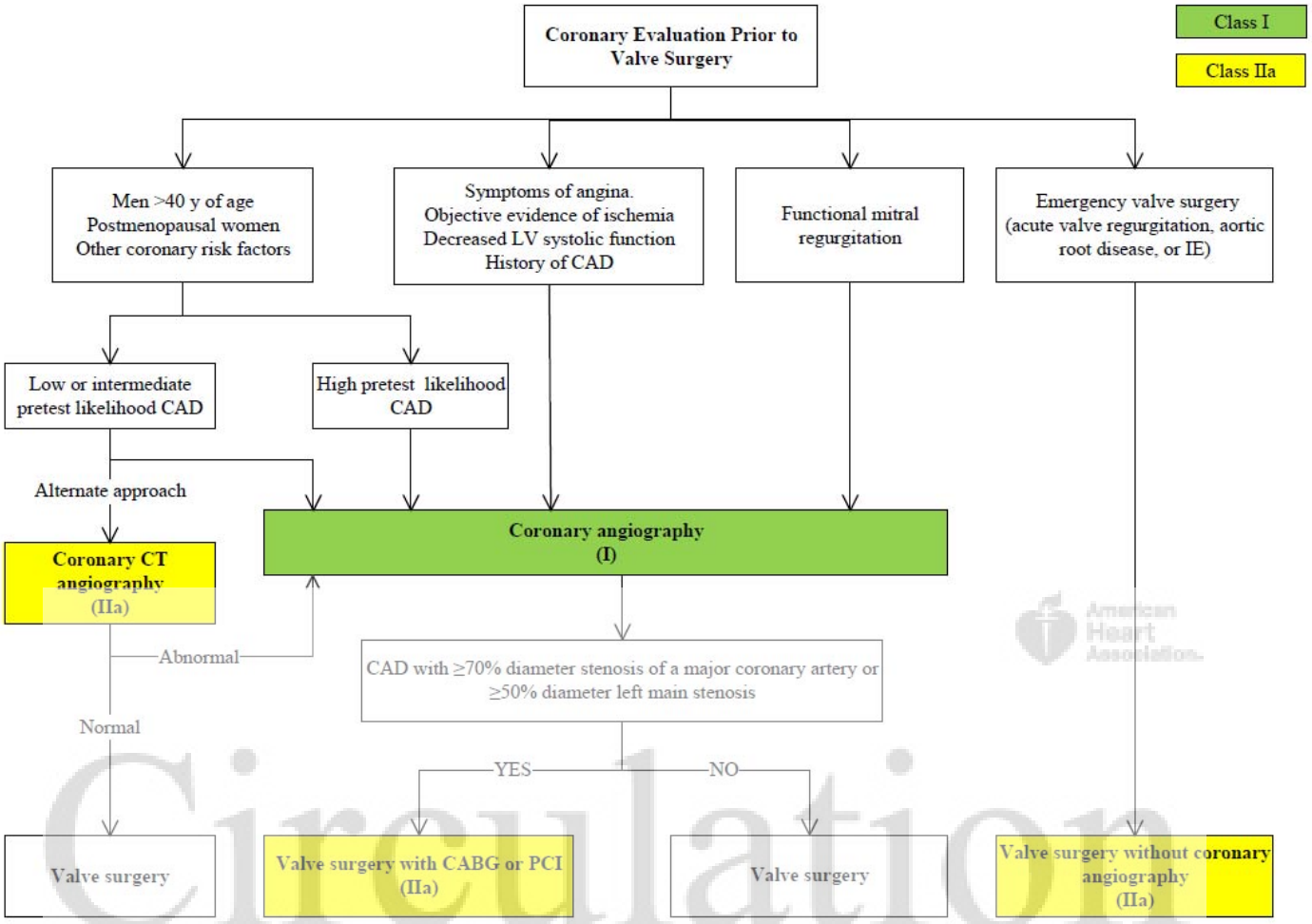

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CT, computed tomography; IE, infective endocarditis; LV, left ventricular; and PCI, percutaneous coronary intervention.

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14.2.2. Intervention for AF: Recommendations

Class IIa

1. **A concomitant maze procedure is reasonable at the time of mitral valve repair or replacement for treatment of chronic, persistent AF. *(Level of Evidence: C)***

The addition of arrhythmia surgery to valve procedures has been advocated on the basis of evidence that persistent AF is an independent risk factor for cerebrovascular accident and mortality following surgery for VHD. When AF has been present for >1 year, stable sinus rhythm is unlikely with mitral repair alone. Arrhythmia procedures span a spectrum from pulmonary vein isolation to the full maze and a variety of intermediate procedures. The term “maze procedure” properly refers to a specific biatrial procedure creating a defined set of conduction block lesions performed “cut and sew” (“maze III”) or with tissue ablation technologies including cryoablative or radiofrequency (“maze IV”). The requisite lesions or incisions include complete encirclement of the pulmonary veins en bloc, an incision or lesion to the mitral annulus from this encircling lesion, and a lesion to the stump of the ligated or amputated left atrial appendage on the LA. On the right atrium, an ablation line or incision extends in the tubular portion from superior vena cava to inferior vena

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cava and along the right atrial free wall from this lateral incision across the body of the right atrium to the tricuspid annulus. A separate incision or lesion extends across the right atrial appendage down to the tricuspid annulus. As originally described, the septum is opened into the fossa ovalis, although this lesion or incision is increasingly omitted in current practice. When performed in this manner, combined with mitral valve repair or replacement, RCTs have shown that the surgical maze procedure affords superior freedom from AF at discharge and at 1 year (with success rates ranging from 75% to 95% with ablation versus 10% to 40% without ablation). Combining the maze procedure with a mitral valve procedure adds little complexity because the LA is already open. As such, the procedure does not appear to significantly increase operative risk of mortality in properly selected patients. In RCTs, long-term survival and stroke risk have not been improved by addition of the maze procedure.

Ligation or amputation of the left atrial appendage is commonly performed in patients with AF with or without such arrhythmia procedures with the aim of reducing the risk of thromboembolic events, although no RCTs have demonstrated a beneficial impact.

Supporting References: (420, 896-912)

Class IIa

2. **A full biatrial maze procedure, when technically feasible, is reasonable at the time of mitral valve surgery, compared with a lesser ablation procedure, in patients with chronic, persistent AF (907, 908). (*Level of Evidence: B)***

A large variety of less extensive procedures, commonly referred to as "mini-maze" procedures, have been developed and promulgated, ranging from pulmonary vein isolation alone to single atrial procedures. The clinical efficacy of these procedures falls below that of the full maze procedure, although the full maze procedure may be associated with more bradycardia requiring pacemaker implantation. Although the less extensive "mini-maze" procedure may be preferable in specific circumstances in which one is willing to trade efficacy for invasiveness, when feasible, the full maze is preferable. These less extensive procedures are more often advocated when the AF is paroxysmal, rather than persistent, and when combined with procedures other than those on the mitral valve.

Supporting References: (907, 908)

Class IIb

1. **A concomitant maze procedure or pulmonary vein isolation may be considered at the time of mitral valve repair or replacement in patients with paroxysmal AF that is symptomatic or associated with a history of embolism on anticoagulation. *(Level of Evidence: C)***

RCTs have shown that the surgical maze procedure affords superior freedom from AF at discharge and at 1 year, defined as sinus rhythm at last follow-up (75% to 95% with ablation versus 10% to 40% without ablation). When the maze procedure is added to mitral valve procedures, it adds little complexity because the LA is already open. As such, this procedure does not appear to increase operative risk of mortality in properly selected patients. In RCTs, neither long-term survival nor stroke risk appears to be improved by addition of the

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procedure. Several nonrandomized studies, however, have suggested a reduction in stroke risk with the addition of the maze procedure to mitral valve repair or MVR even when a mechanical prosthesis is used.

Other surgical approaches to prevention of recurrent AF, including less extensive procedures such as pulmonary vein isolation or a left-sided-only maze, have been less successful than the full maze procedure in converting the patient to sinus rhythm. Although less effective, these less extensive procedures are also less invasive and, accordingly, are more often advocated when the AF is paroxysmal rather than persistent and when combined with procedures other than those on the mitral valve.

Supporting References: (898, 900-902, 904-906, 913, 914)

Class IIb

2. **Concomitant maze procedure or pulmonary vein isolation may be considered at the time of cardiac surgical procedures other than mitral valve surgery in patients with paroxysmal or persistent AF that is symptomatic or associated with a history of emboli on anticoagulation. *(Level of Evidence: C)***

The addition of arrhythmia surgery to valve procedures other than mitral valve disease has been advocated on the basis of evidence that persistent AF is an independent risk factor for cerebrovascular accident and mortality following surgery for mitral VHD. Limited data suggest an increased risk of HF and stroke after AVR as well. When combined with aortic valve surgery, the addition of the maze procedure has been shown in observational studies to improve conversion to sinus rhythm over aortic valve surgery alone. This occurs in the setting of chronic AF without a statistically significant increase in operative risk of mortality, although the potential impact of selection bias cannot be ignored. Limited evidence suggests pulmonary vein isolation is equivalent to maze in the presence of paroxysmal AF.

Supporting References: (420, 896, 897, 915)

Class III: No Benefit

1. **Catheter ablation for AF should not be performed in patients with severe MR when mitral repair or replacement is anticipated, with preference for the combined maze procedure plus mitral valve repair (916). *(Level of Evidence: B)***

A single randomized study of patients with rheumatic mitral valve disease compared catheter ablation with surgical maze and demonstrated superior conversion to sinus rhythm (82% versus 55%) in the surgical group. Accordingly, if surgical repair or replacement of the mitral valve is anticipated, catheter ablation should be deferred in favor of surgical maze.

Supporting References: (916)

See Online Data Supplement 27 for more information on the maze procedure
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

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15. Noncardiac Surgery in Patients With VHD

15.1. Diagnosis and Follow-Up

The risk of noncardiac surgery is increased in patients with significant VHD. AS is present in 1% to 2% of all patients >65 years of age and 3% to 8% of all patients >75 years of age. Severe AS is associated with an increased risk for noncardiac surgery, depending on the specific degree of valve narrowing, LV systolic function, concurrent CAD, and other risk factors for surgery. The estimated rate of cardiac complications in patients with undiagnosed severe AS undergoing noncardiac surgery is 10% to 30%. Thus, TTE is appropriate in patients being evaluated for noncardiac surgery when a systolic murmur suggestive of AS is present for evaluation of stenosis severity and LV systolic function to allow optimization of perioperative management. Evaluation for concurrent CAD in patients with AS is problematic, and standard ECG exercise testing is not adequate. A stress echocardiographic or nuclear imaging study may be helpful if resting LV systolic function is normal and AS is only mild to moderate in severity. With severe AS, coronary angiography may be necessary if risk factors or symptoms that might be due to coronary disease are present.

MS may also be poorly tolerated with the altered hemodynamics of anesthesia and noncardiac surgery. Left-sided regurgitant lesions are better tolerated but still convey increased risk, particularly if the anesthesiologist and surgeon are unaware of the diagnosis or severity of valve disease. Thus, whenever the clinical history or physical examination suggests valve disease might be present, TTE is helpful to detect valve dysfunction and quantitate the severity of stenosis and regurgitation. Other echocardiographic data useful in operative planning include LV systolic function and an estimate of pulmonary artery systolic pressure.

Supporting References: (917-923)

15.2. Medical Therapy

Anesthetic management of patients with VHD undergoing noncardiac surgery should take into account the underlying valvular abnormality, its effect on the systolic and diastolic function of the heart, and any comorbidities, such as CAD or pulmonary hypertension. In noncardiac surgical patients with AS, the reduced LV compliance that results from the chronic pressure overload makes ventricular filling dependent on preload and atrial contraction. In the patient with AS, arrhythmias are poorly tolerated. Specifically, tachycardia should be particularly avoided, because the combination of a shortened diastolic filling period and a stiff left ventricle results in inadequate LV filling and a fall in cardiac output. If possible, sinus rhythm should be maintained and the ventricular rate controlled. A typical example is the patient with AS with acute onset supraventricular tachycardia or AF, in whom synchronized cardioversion should be applied immediately if the patient becomes hypotensive. The atrial contribution to LV filling is often significant, particularly with AS and diastolic dysfunction. Intravascular volume should be titrated at a level that ensures an adequate forward cardiac output without an excessive rise in left atrial pressure. This can be achieved by ensuring adequate volume replacement with guidance from central venous or pulmonary pressures or dynamic pulsatility indices, and monitoring LV chamber size with intraoperative TEE may be particularly useful. A drop in systemic vascular resistance may

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reduce diastolic BP and coronary blood flow, leading to myocardial ischemia, and this may be particularly detrimental in the patient with coexisting CAD or peripheral artery disease. The anesthetic approach and anesthetic agents should be chosen to avoid systemic hypotension. Potential detrimental effects of the anesthetic approach should be considered, such as acute increases in afterload-induced laryngoscopy, tracheal intubation, or surgical stimulation. Either phenylephrine or norepinephrine can be used to raise the BP; both were found to not adversely affect LV systolic and diastolic function. Instances of systemic hypertension should be treated preferentially with arterial dilators, such as short-acting calcium channel blockers instead of preload-reducing agents such as nitroglycerin. General anesthetics are well tolerated, and the choice of anesthetic agents should be carefully titrated to maintain normotension and sinus rhythm. It is equally important to modify epidural or spinal anesthetic interventions so that systemic pressure changes do not occur or occur gradually. For example, only high-dilution neuraxial local anesthetic agents in combination with opioids should be used.

The patient with MS undergoing noncardiac surgery should be treated in a manner similar to the patient with AS, because the pathophysiology of the disease and its implications are similar. Maintenance of normal LV preload, sinus rhythm, and avoidance of tachycardia and systemic hypotension should be the targets in the perioperative period. Of particular concern is judicious intravenous fluid administration so as to avoid increases in the left atrial pressure and pulmonary capillary pressure that may precipitate acute pulmonary edema.

Patients with AR or MR present with chronic LV volume overload. In either disease, a decrease in systemic afterload will augment the systemic LV output and reduce the regurgitant volume. Patients with regurgitant valve lesions are better suited to receive a regional anesthetic, because the combination of neuraxial local anesthetics and opioids produces a favorable systemic vasodilation. However, preload should be maintained, particularly in the chronic regurgitation lesions, because there is a larger LV volume and increase in diastolic compliance. Monitoring of central venous or pulmonary pressures and size and function of the left ventricle should be done with invasive catheters or echocardiography.

Changes in fluid balance continue to occur postoperatively, so these intraoperative considerations are applicable in the 48- to 72-hour postoperative period as well as during the procedure.

Supporting References: (924-929)

15.3. Intervention: Recommendations

When VHD is diagnosed in patients being considered for elective noncardiac surgery, the first step is to review the standard criteria for intervention of the specific valve lesion. If the patient meets standard criteria for intervention, it is usually prudent to defer the elective noncardiac procedure and proceed to valve intervention instead.

In patients with significant asymptomatic valve disease who do not meet standard criteria for intervention, the risk of the noncardiac procedure can be minimized by 1) having an accurate diagnosis of the type and severity of valve dysfunction, 2) choosing an anesthetic approach appropriate to the valve lesion, and 3) ensuring a higher level of intraoperative monitoring.

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In emergency situations, noncardiac surgery may be necessary in the presence of uncorrected severe valve disease. In patients with severe AS or MS, volume shifts and rhythm disturbances associated with the surgical stress and cardiovascular side effects of the anesthetic medications may lead to hypovolemia and tachycardia and further hemodynamic compromise. Thus, patients with severe left-sided valve stenosis requiring emergency noncardiac surgery should be managed by a cardiovascular anesthesiologist with invasive hemodynamic or TEE imaging monitoring intraoperatively and remain in an intensive monitoring setting for 48 to 72 hours postoperatively.

Class IIa

1. **Moderate-risk elective noncardiac surgery with appropriate intraoperative and postoperative hemodynamic monitoring is reasonable to perform in patients with asymptomatic severe AS (917, 920-922).** ***(Level of Evidence: B)***

The hemodynamic effects of anesthesia and surgery are poorly tolerated in patients with severe AS. AVR is recommended in all patients with symptomatic severe AS and should be performed before other surgical interventions to avoid hemodynamic instability during, as well as after, noncardiac surgery.

In patients with moderate-to-severe AS, 30-day mortality is higher for patients with AS (2.1%) compared with propensity score–matched controls (1.0%) with a higher risk of postoperative MI in patients with AS. Predictors of adverse outcomes include severity of AS, high-risk surgery, cardiac symptoms, coexisting MR, and CAD. However, these comorbidities also increase the risk of AVR. The risk–benefit ratio continues to favor managing patients with severe AS undergoing moderate-risk noncardiac surgery with hemodynamic monitoring and optimization of loading conditions rather than considering prophylactic AVR.

Adverse outcomes in the setting of aortic valve obstruction are due to the combination of the anesthetic procedure (general, regional, or monitored anesthesia care) and surgical stress. Systemic hypotension and tachycardia may result in decreased coronary perfusion pressure, development of arrhythmias or ischemia, myocardial injury, cardiac failure, and death. These complications can be avoided by periprocedural hemodynamic monitoring with a right-heart catheter or intraoperative TEE to allow continuous optimization of loading conditions. Intra- and postoperative monitoring of BP and intracardiac volume are implemented starting in the preoperative period and continuing until hemodynamics are stable, which may be as long as 24 to 48 hours after the procedure. Maintenance of normal coronary perfusion pressure with the administration of alpha-adrenergic agents, such as phenylephrine, may be helpful early in the procedure to avoid the detrimental consequences of myocardial hypoperfusion.

Supporting References: (917, 920-922)

Class IIa

2. **Moderate-risk elective noncardiac surgery with appropriate intraoperative and postoperative hemodynamic monitoring is reasonable to perform in patients with asymptomatic severe MR.** ***(Level of Evidence: C)***

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In patients with severe MR undergoing noncardiac surgery, the overall hemodynamic goals are avoidance of both increased afterload and bradycardia by choosing the appropriate anesthetic scheme. Invasive hemodynamic and/or TEE monitoring allows for continuous optimization of loading conditions during and after the operative procedure, with these patients admitted to an intensive monitoring setting for up to 24 to 48 hours after the procedure.

Supporting Reference: (930)

Class IIa

3. **Moderate-risk elective noncardiac surgery with appropriate intraoperative and postoperative hemodynamic monitoring is reasonable to perform in patients with asymptomatic severe AR and a normal LVEF. *(Level of Evidence: C)***

Patients with severe AR are prone to hemodynamic instability because of the detrimental effects of increased volume on myocardial wall stress. The perioperative stress associated with noncardiac surgery may lead to hypotension, arrhythmias, HF, or even death. It is especially important to avoid bradycardia when AR is present due to the increase in total diastolic time. These patients should be monitored with invasive systemic arterial and venous catheters and/or TEE and admitted postoperatively to an intensive monitoring setting. Patients with severe AR and a decreased LVEF, elevated serum creatinine >2 mg/dL, or who are undergoing intermediate- to high-risk noncardiac surgery have the highest risk of cardiopulmonary complications and death.

Supporting Reference: (931)

Class IIb

1. **Moderate-risk elective noncardiac surgery in patients with appropriate intraoperative and postoperative hemodynamic monitoring may be reasonable to perform in asymptomatic patients with severe MS if valve morphology is not favorable for percutaneous balloon mitral commissurotomy. *(Level of Evidence: C)***

Patients with asymptomatic severe MS and valve anatomy favorable for percutaneous balloon mitral commissurotomy who are undergoing elective noncardiac surgery should be evaluated and treated pursuant to the recommendations for MS (Section 4.2.3). If valve anatomy is not favorable or if there are other contraindications to percutaneous balloon mitral commissurotomy, elective noncardiac surgery may be considered with invasive hemodynamic monitoring to optimize loading conditions. Preload should be maintained high enough to allow an adequate forward cardiac output across the stenotic mitral valve but low enough to avoid pulmonary edema. Maintaining preload in this narrow range can be challenging and requires measurement of cardiac output and pulmonary wedge pressure. Tachycardia should be avoided due to the shortened diastolic LV filling time across the stenotic mitral valve, resulting in an increase in left atrial pressure.

Supporting References: (924, 932)

See Online Data Supplement 28 for more information on noncardiac surgery
(http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000031/-/DC1).

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16. Evidence Gaps and Future Directions

Current recommendations for evaluation and management of VHD are largely based on clinical experience and observational studies, with few prospective RCTs. We recommend that research on valve disease span the spectrum from basic science to prospective randomized trials and that studies focus on each stage of the disease process from the patient at risk to the patient with end-stage disease.

16.1. Prevention of Valve Disease—Stage A

On a worldwide basis, rheumatic fever remains the primary cause of VHD; global health systems outcomes studies are needed to identify impediments to successful primary and secondary prevention of rheumatic heart disease. Other approaches to prevention (such as vaccine development) and delaying disease progression once valve damage is present should also be explored. Disease prevention in patients at risk of other types of valve disease is needed. Some subgroups at risk of calcific AS can be identified, such as those with a congenital bicuspid aortic valve or elevated lipoprotein(a) levels. However, there are no known therapies to prevent valve dysfunction in these patients. Basic science studies on the genetic and pathobiological causes of valve dysfunction will provide insight into mechanisms of disease initiation and progression that might be amenable to medical therapy.

Supporting References: (933-938)

16.2. Medical Therapy to Treat or Prevent Disease Progression—Stage B

In patients with early VHD, including those with calcific or myxomatous disease, there are currently no therapies to prevent disease progression in the valve leaflets. Instead, our recommendations are all directed toward patient monitoring with the intent to intervene once severe disease is present that results in symptoms or abnormal cardiovascular function. Again, basic science studies are needed to identify potential targets for prevention of progressive VHD that then can be translated into prospective clinical trials. Additional studies are needed for therapies that might prevent the adverse consequences of VHD, such as LV dysfunction and pulmonary hypertension.

Supporting Reference: (939)

16.3. Optimal Timing of Intervention—Stage C

Current approaches to identifying the optimal timing of intervention in patients with progressive valve disease are suboptimal. Symptom onset is a subjective measure and may occur too late in the disease course for optimal long-term outcomes. Despite the availability of sophisticated approaches for measurement of LV volumes, systolic function, diastolic function, and other measures of myocardial performance, recommendations rely only on simple linear dimensions used in published series with data that may not reflect contemporary clinical outcomes. We urgently need studies evaluating the value of newer measures of LV size, function, and myocardial structure in predicting outcomes after valve intervention. However, LV enlargement and dysfunction are late consequences of valve dysfunction; as more durable approaches to restoring normal valve function are

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developed, the balance of benefit–risk for intervention will shift to earlier in the disease. Studies examining the role of earlier markers of myocardial dysfunction such as strain and strain-rate imaging, diastolic dysfunction, serum markers, and other novel approaches to defining the optimal timing of intervention also are needed.

Few studies have included adequate numbers of older adults to make specific recommendations for this group of patients in whom particular concerns, such as cognitive function, frailty, and mobility challenges, may change the decision algorithms.

Given the relatively low risk of intervention in otherwise healthy patients and the improved options for valve repair or replacement, RCTs of intervention for severe asymptomatic VHD are needed. Examples of specific conditions where clinical equipoise exists are asymptomatic severe AS in otherwise healthy patients, asymptomatic severe AR with normal LV systolic function, and severe *primary* MR with normal LV function and a high likelihood of valve repair. Data from large, carefully designed registries are also needed for defining and improving quality of care.

16.4. Better Options for Intervention—Stage D

We need better options for valve repair and replacement. The timing of intervention is based on the balance between outcomes with native valve disease and the risk and long-term durability of the valve after intervention. As valve repair and replacement options improve, the balance will shift toward earlier intervention. We need a valve substitute that can be safely and reliably implanted, is nonthrombogenic, has hemodynamics similar to a normal native valve, and is durable. Transcatheter valve procedures offer the promise of safe implantation and excellent hemodynamics, but long-term durability is not yet known. In patients who require mechanical valve replacement, we need oral therapy that provides effective anticoagulation with a low risk of complications and no negative impact on quality of life.

Moderate-to-severe VHD is present in 2.5% of the U.S. population and increases in prevalence with age. The disease affects between 4% and 9% of those 65 to 75 years of age and 12% to 13% of those >75 years of age. Many of these patients require surgical or interventional procedures. However, even with intervention, overall survival is lower than expected, and the risk of adverse outcomes due to VHD is high, both because of limited options for restoring normal valve function and failure to intervene at the optimal time point in the disease course. We urgently need research on almost every aspect of VHD to ensure that patients who already have VHD receive optimal therapy and to prevent VHD in those at risk. Approaches to improving outcomes in patients with VHD include 1) national and international registries and RCTs, 2) continuous evaluation of outcomes data at each Heart Valve Center of Excellence, and 3) focus on patient-centric care with involvement of the patient in the decision-making process.

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Key Words: ACC/AHA Practice Guidelines ■ anticoagulation therapy ■ aortic stenosis ■ aortic regurgitation ■ bicuspid aortic valve ■ cardiac surgery ■ heart valves ■ infective endocarditis ■ mitral stenosis ■ mitral regurgitation ■ prosthetic valves ■ pulmonic regurgitation ■ pulmonic stenosis ■ transcatheter aortic valve replacement ■ tricuspid stenosis ■ tricuspid regurgitation ■ valvular heart disease.

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)–2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Rick A. Nishimura, *Co-Chair*	Mayo Clinic, Division of Cardiovascular Disease—Judd and Mary Morris Leighton Professor of Medicine	None	None	None	None	None	None	None
Catherine M. Otto, *Co-Chair*	University of Washington Division of Cardiology—Professor of Medicine	None	None	None	None	None	None	None
Robert O. Bonow	Northwestern University Medical School—Goldberg Distinguished Professor	None	None	None	None	None	None	None
Blasé A. Carabello	VA Medical Center—Professor of Medicine, Baylor College of Medicine	None	None	None	None	• Edwards Lifesciences (DSMB)† • Medtronic†	None	2.4.2, 3.2.3, 3.2.4, 4.3.3, 5.1.3, 6.2.3, 7.3.1.1, 7.3.3, 7.4.3, 8.2.3, 11.1.1, 11.1.2, 11.2.2, 11.3.2, 11.4, 11.6.1, 11.6.2, 11.6.3, 11.7.3, 11.8.3, 12.2.1, 12.2.3, 13.1, 13.1.2, 13.1.3, 13.2.1, 13.2.3, 13.3.1, 13.3.2, 14.1, and 14.2.2.
John P. Erwin, III	Scott and White Hospital and Clinic—Senior Staff Cardiologist, Associate Professor of Medicine	None	None	None	None	None	None	None
Robert A. Guyton	Emory Clinic, Inc.—Professor and Chief, Division of Cardiothoracic Surgery	• Medtronic	None	None	None	None	• Defendant, Cardiac Surgery, 2013	2.4.2, 3.2.3, 3.2.4, 4.3.3, 5.1.3, 6.2.3, 7.3.1.1, 7.3.3, 7.4.3, 8.2.3, 11.1.1, 11.1.2, 11.2.2, 11.3.2, 11.4,

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								11.6.1, 11.6.2, 11.6.3, 11.7.3, 11.8.3, 12.2.1, 12.2.3, 13.1, 13.1.2, 13.1.3, 13.2.1, 13.2.3, 13.3.1, 13.3.2, 14.1, and 14.2.2.
Patrick T. O'Gara	Brigham and Women's Hospital—Professor of Medicine; Harvard Medical School—Director of Clinical Cardiology	None	None	None	None	None	None	None
Carlos E. Ruiz	Lenox Hill Heart and Vascular Institute of New York—Professor and Chief, Division of Pediatric Cardiology	None	None	None	None	None	None	None
Nikolaos J. Skubas	Weill Cornell Medical College—Associate Professor of Anesthesiology and Director of Cardiac Anesthesia	None	None	None	None	None	None	None
Paul Sorajja	Mayo Clinic—Associate Professor of Medicine	None	None	• Intellectual property in patent on percutaneous closure of paravalvular prosthetic regurgitation	None	None	None	None
Thoralf M. Sundt, III	Massachusetts General Hospital—Chief, Division Cardiac Surgery	• St. Jude Medical	None	None	None	None	• AATS, Secretary-Elect	2.4.2, 3.2.3, 3.2.4, 4.3.3, 5.1.3, 6.2.3, 7.3.1.1, 7.3.3, 7.4.3, 8.2.3, 11.1.1, 11.1.2, 11.2.2, 11.3.2, 11.4, 11.6.1, 11.6.2, 11.6.3, 11.7.3, 11.8.3, 12.2.1, 12.2.3, 13.1, 13.1.2, 13.1.3, 13.2.1, 13.2.3, 13.3.1, 13.3.2, 14.1,

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								and 14.2.2.
James D. Thomas	Cleveland Clinic—Professor of Medicine and Biomedical Engineering	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.
†No financial benefit.

AATS indicates American Association of Thoracic Surgery; DSMB, data safety monitoring board; and VA, Veterans Affair.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)–2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Blair D. Erb	Official Reviewer—ACC Board of Trustees	Bozeman Deaconess Hospital, Cardiology Consultants—Physician	None	None	None	None	• Medtronic	None
Mario J. Garcia	Official Reviewer—AHA	Montefiore Medical Center-Albert Einstein	None	None	None	None	• Medtronic† • Pfizer	None

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Appendix 3. Abbreviations

2D = 2-dimensional

3D = 3-dimensional

ACE = angiotensin-converting enzyme

AF = atrial fibrillation

ARB = angiotensin-receptor blocker

aPTT = activated partial thromboplastin time

AR = aortic regurgitation

AS = aortic stenosis

AVR = aortic valve replacement

BP = blood pressure

CABG = coronary artery bypass graft

CAD = coronary artery disease

CMR = cardiac magnetic resonance

COR = Class of Recommendation

CT = computed tomography

ECG = electrocardiogram

HF = heart failure

HIV = human immunodeficiency virus

IE = infective endocarditis

INR = international normalized ratio

LA = left atrium

LMWH = low-molecular-weight heparin

LOE = Level of Evidence

LV = left ventricular

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic dimension

MI = myocardial infarction

MR = mitral regurgitation

MS = mitral stenosis

MVR = mitral valve replacement

NYHA = New York Heart Association

NVE = native valve endocarditis

PR = pulmonic regurgitation

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PROM = predicted risk of mortality

PVE = prosthetic valve endocarditis

RCT = randomized controlled trial

RV = right ventricular

TAVR = transcatheter aortic valve replacement

TR = tricuspid regurgitation

TS = tricuspid stenosis

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography/echocardiogram

UFH = unfractionated heparin

VHD = valvular heart disease

VKA = vitamin K antagonist

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(Section numbers correspond to the full-text guideline.)

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Data Supplement 1. Outcomes in Adults With Low-Flow/Low-Gradient Aortic Stenosis With Reduced Left Ventricular Ejection Fraction (stage S1) (Sections 3.2.1.1 and 3.2.3)

Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
DeFillippi, 1995 (1) 7810504	To determine if DSE can distinguish severe fixed AS from flow-dependent AS	Prospective	24	AVAi ≤0.5 cm^2/m^2 ΔP_{mean} ≤30 mm Hg LVEF ≤45% All symptomatic	Too ill AF	**IA**. (n=7, 39%) No change in AVA with ≥20% improvement in LVEF (contractile reserve). **IB**. (n=5, 28%) ↑AVA ≥0.3 cm^2 and contractile reserve. **II**. (n=6, 33%) No contractile reserve.	**IA.** 4 underwent AVR with improved symptoms (1 perioperative death). **IB.** 4 medical Rx and alive at 1 y. 1 CAD death. **II.** 3 deaths and 3 persistent CHF.
Connolly, 1997 (2) 9170402	Determine outcome after AVR for severe AS with LG and low LVEF	Retrospective surgical database	154	LVEF ≤35% Undergoing AVR	Other valve disease	Baseline mean AVA 0.6±0.2 cm^2, Mean cardiac output 4.1±1.5 L/min, Perioperative (30 d) mortality 9%, Postoperative LVEF improved in 76% of pts.	Study group had low LVEF, but not all had LG or LF.
Pereira, 2002 (3) 11955855	Evaluate outcome with AVR vs. medical Rx in LFLG severe AS	Retrospective, propensity score matched	68	AVA ≤0.75 cm^2 ΔP_{mean} ≤30 mm Hg LVEF ≤35%	Other valve disease.	In propensity matched pts, survival at 4 y was 78% with AVR vs.15% with medical Rx (p<0.0001).	Multivariate predictors of survival were AVR, age, and renal function.
Nishimura, 2002 (4) 12176952	Diagnostic value of invasive hemodynamics with dobutamine stress	Prospective, comparison with surgical findings	32	AVA <1.0 cm^2 ΔP_{mean} <40 mm Hg LVEF <40%	N/A	With dobutamine, final AVA ≤1.2 cm^2 with a ΔP_{mean} >30 mm Hg in 21 pts; severe AS confirmed at surgery. In 15 pts with CR, mortality was 7% (1 death) with medical therapy.	CR defined as ↑SV ≥20% with dobutamine.
Monin, 2003 (5) 12835219	Assess prognostic value of DSE in LFLG AS	Prospective, multicenter	136	AVA ≤1.0 cm^2 Cardiac index ≤3 $L/min/m^2$ ΔP_{mean} ≤40 mm Hg	Other valve disease, severe comorbidities	Operative mortality 5% with CR vs. 32% without CR (p=0.0002). Predictors of long-term survival were AVR and CR.	CR defined as ↑SV ≥20% on DSE.
Quere, 2006 (6) 16585393	Determine relationship between CR on DSE and postoperative LVEF	Prospective, multicenter	66	AVA ≤1.0 cm^2 ΔP_{mean} ≤40 mm Hg LVEF ≤40% All symptomatic	Excluded operative deaths	**I**. CR in 70%; post-AVR LVEF improved ≥10 LVEF units in 83%. **II**. No contractile reserve in 30%; post-AVR LVEF improved ≥10 LVEF units in 65%.	Symptoms improved by ≥2 classes after AVR in 58%. Mean LVEF increased from 29±6% to 47±11% after AVR.
Blais, 2006 (7) 16461844	Improve differentiation of true from pseudo severe AS on DSE	In vitro model and prospective pt group	23	AVAi ≤0.6 cm^2/m^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg All symptomatic undergoing AVR	Other valve disease AF or paced rhythm	Projected effective orifice area at a normal transvalvular flow rate was accurate for identifying true vs. pseudo severe AS in comparison to surgical findings.	No outcome data.
Bergler-Klein, 2007 (8) 15117847	Relationship between BNP and outcome in LFLG AS	Prospective, multicenter	69	AVAi <0.6 cm^2/m^2 ΔP_{mean} ≤40 mm Hg LVEF ≤40%	Other valve disease, AF, or paced rhythm	BNP was higher with true-severe AS compared to pseudo-severe AS (p=0.12). 1-y survival 47±9% with BNP ≥550 pg/mL vs. 97±3% with BNP <550 pg/mL (p=0.0001).	Classified as severe AS if DSE showed AVA ≤1.0 cm^2 at projected flow rate of 250 mL/s; pseudo-severe if AVA >1.0 cm^2 projected at 250 mL/s.

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Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
Pai, 2008 (9) 19021976	Surgical outcome with low-gradient AS	Retrospective surgical database	362	AVA ≤0.8 cm^2 *AND* ΔP_{mean} ≤30 mm Hg *OR* LVEF ≤35%	N/A	In 194 pts with LVEF ≤35%, 5-y survival was 50% with AVR vs. 23% without AVR (p<0.0001). In 168 pts with ΔP_{mean} ≤30 mm Hg, 5-y survival was 80% with AVR vs. 22% without AVR (p<0.0001).	Univariate predictors of mortality were older age, lower LVEF, renal insufficiency, and lack of AVR.
Levy, 2008 (10) 18402902	Evaluate perioperative mortality with LFLG severe AS	Surgical series AVR for LGLF AS	217	AVA <1 cm^2 LVEF ≤35% ΔP_{mean} ≤30 mm Hg	Other valve disease	Perioperative mortality 16% overall (decreased from 20% in 1990s to 10% after 2000). 5-y survival was 49±4%.	Predictors of perioperative mortality were very LG, multivessel CAD, and absence of CR on DSE.
Clavel, 2010 (11) 20975002	Compare outcomes after TAVR vs. SAVR with low LVEF severe AS	Prospective comparison of echo data	200 SAVR; 83 TAVR	AVA ≤1 cm^2 LVEF ≤50%	No LVEF by echo	LVEF improved more with TAVR compared to SAVR (ΔLVEF, 14±15% vs. 7±11%; p=0.005). At 1 y, LVEF was normal in 58% of TAVR compared to 20% SAVR pts.	Treatment not randomized.
Tribouilloy, 2009 (12) 19442886	Effect of AVR on outcomes in LFLG severe AS without contractile reserve	Prospective, multicenter	81	AVA <1 cm^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg No contractile reserve	N/A	Survival at 5 y was higher with AVR compared to medical therapy (54±7% vs. 13±7%; p=0.001). Operative mortality was 22% (n=12).	Contractile reserve defined as ↑SV ≥20% on DSE. Multivariate predictors of mortality were associated bypass surgery (p=0.007) and ΔP_{mean} ≤20 mm Hg (p=0.035).
Gotzmann, 2012 (13) 21805576	Outcomes after TAVR with low LVEF and LG AS	Prospective CoreValve TAVR	202	LVEF groups >50% or ≤50% ΔP_{mean} groups >40 or ≤40 mm Hg	N/A	1 y mortality: *LVEF >50%*	*LVEF ≤50%* *ΔP_{mean} >40*: 14% (n=86)	27% (n=45) *ΔP_{mean} ≤40*: 22% (n=27)	39% (n=44)	1-y mortality after TAVR was higher with LG, low LVEF severe AS. Severe AS defined as AVA ≤1.0 cm^2. All pts were high surgical risk.
Fougeres, 2012 (14) 22733832	Outcome of pseudo-severe AS without AVR	Multicenter registry of severe symptomatic LFLG AS	107	AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg Cardiac index ≤3.0 L/min/m^2	Severe comorbidities, Other valve disease, AF	**IA**: 43 with true-severe AS **IB:** 29 with pseudo-severe AS defined as CR with final AVA ≥1.2 cm^2 and ΔP_{mean} ≤40 mm Hg **II:** 23 with no CR (↑SV <20%)	74 deaths (69%) at a median interval of 10 m. Outcomes with pseudo-severe AS (Group IB) were similar to pts with HF without AS. Multivariate predictors of mortality in Group 1B were CAD (HR: 1.88; 95% CI: 1.35–2.63) and ΔP_{mean} <20 mm Hg (HR: 1.55; 95% CI: 1.07–02.23).
Herrmann 2013 (15) 23661722	Surgical vs. transcatheter AVR for in operable pts with LFLG severe AS with	Subgroup analysis of RCT	42 randomized to TAVR vs.	AVA ≤0.8 cm^2 or AVAi <0.5 cm^2/m^2 LVEF <50%	N/A	Mortality at 2 y was 80.0% with medical therapy vs. 47.1% with TAVR (HR: 0.43; 95% CI: 0.19–0.98; p=0.040)	No difference in 2-y outcomes in the 105 pts with LFLG severe AS with low LVEF randomized to SAVR vs.

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Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
	reduced LVEF		medical Rx	ΔP_{mean} ≤40 mm Hg SVi < 35 mL/m^2			TAVR (42.9% vs. 37.1%; HR: 1.25, 95% CI: 0.66–2.36; p=0.50).

AF indicates atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; BNP, brain natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CR, contractile reserve; DSE, dobutamine stress echocardiography; HF, heart failure; LFLG, low-flow/low-gradient; LF, low flow; LG, low gradient; N/A, nonapplicable; ΔP_{mean}, mean transaortic systolic pressure gradient; pts, adult patients; Rx, prescription; rLVEF, left ventricular reduced ejection fraction; ΔP_{mean} , mean transaortic pressure gradient; SAVR, surgical aortic valve replacement; SV, stroke volume; SVi, stroke volume indexed to body surface area; and TAVR, transcatheter aortic valve replacement.

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Data Supplement 2. Hemodynamic Progression of Aortic Stenosis in Adult Patients (stages B and C) (Section 3.2.1.3)

First Author, Year	N	Type of Study	Entry Criteria	Mean Follow-up (y)	Increase in ΔP_{mean} (mmHg/y) (mean± SD)	Increase in V_{max} (m/s/y) (mean± SD)	Decrease in AVA (cm^2/y) (mean± SD)
Otto, 1989 (16) 2918158	42	Prospective	Asymptomatic; V_{max} >2.5 m/s	1.7	8 (-7–23)	0.36±0.31	0.1
Roger, 1990 (17) 2301222	112	Retrospective	AS on echo	2.1	N/A	0.23±0.37	N/A
Faggiano, 1992 (18) 1626512	45	Prospective	AS on echo	1.5	N/A	0.4±0.3	0.1±0.13
Peter, 1993 (19) 8404089	49	Retrospective	AS on echo	2.7	7.2	N/A	N/A
Brener, 1995 (20) 7829781	394	Retrospective	AS on echo	6.3	N/A	N/A	0.14
Otto, 1997 (21) 9142003	123	Prospective	Asymptomatic, V_{max} >2.5 m/s	2.5	7±7	0.32±0.34	0.12±0.19
Bahler, 1999 (22) 10569661	91	Retrospective	AS on echo	1.8	2.8	0.2	0.04
Palta, 2000 (23) 10831524	170	Retrospective	AS on echo	1.9	N/A	N/A	0.10±0.27
Rosenhek, 2000 (24) 10965007	128	Prospective	V_{max} >4.0m/s	1.8	Slow	0.14±0.18	N/A
					Rapid	0.45±0.38	N/A
Rosenhek, 2004 (25) 14972419	176	Retrospective	V_{max} 2.5–3.9 m/s	3.8	N/A	0.24±0.30	N/A
Rossebo, 2008 (26) 18765433	1,875	Prospective	V_{max} 2.5–4 m/s	4.3	Statin Rx	0.15±0.01	0.03±0.1
					Placebo	0.16±0.01	0.03±0.1

AS indicates aortic stenosis; AVA, aortic valve area; echo, echocardiography; N/A, not applicable; ΔP_{mean}, mean transaortic pressure gradient; V_{max}, maximum velocity.

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Data Supplement 3. Exercise Stress Testing in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Sections 3.2.1.5 and 3.2.3)

Study	Aim of Study	Study Type	Study Size	Inclusion Criteria	Exclusion Criteria	Exercise Findings/Clinical Outcomes	Comments
Nylander, 1986 (27) 3707789	Describe hemodynamics, clinical features, noninvasive findings in elderly pts with suspected severe symptomatic AS	Observational, exercise test	76 (37 in NHYA class III/IV)	Suspected symptomatic severe AS, Mean age 65 y	N/A	Inadequate BP increase with exercise in 82%. ETT was at variance with reported NYHA class in 25%. Exercise tolerance was <80% expected for age.	ETT stopped for low BP in 36% and chest pain in 29%. No clinical outcome data. Most pts were symptomatic at baseline.
Clyne, 1991 (28) 1746429	Evaluate exercise response	ETT, Thallium perfusion imaging, MUGA	14	Asymptomatic AS	N/A	AS pts had decreased exercise tolerance and VO_{2max} vs. controls	ST depression >1 mm flat or downsloping in 71%. Reversible perfusion defect in 21%. ↓BP >10 mm Hg in 7%. No clinical outcome data.
Otto, 1992 (29) 1401617	Measure physiologic response to exercise	Prospective, Bruce protocol ETT, Doppler echo	28	Asymptomatic AS	N/A	Exercise duration 6.7±4.3 min V_{max} ↑3.99±0.93 to 4.61±1.12 m/s (p<0.0001) ΔP_{mean} ↑39±20 to 52±26 mm Hg (p<0.0001) Stroke volume ↓98±29 to 89±32 mL (p=0.01) Q_{max} ↑422±117 to 523±209 mL/s (p<0.0001) SEP ↓0.33±0.04 to 0.24±0.002 (p<0.0001) Cardiac output ↑6.5±1.7 to 10.2 4.4 L/min (p<0.0001) AVA 1.17±0.45 to 1.28±0.65 (p=NS)	↓BP >10 mm Hg in 11%. ST depression >1 mm flat or downsloping in 75%. Occasional PVCS in 39%. Asymptomatic 3-beat VT in 4% (1 pt.). No clinical outcome data.
Otto, 1997 (21) 9142003	Identify predictors of clinical outcome	Prospective, clinical, echo, and ETT data	104 pts 274 exercise tests	Asymptomatic AS (V_{max} >2.5 m/s)	Unable to walk on treadmill	Univariate predictors of clinical outcome (AVR or death) included a smaller exercise ↑AVA, BP, and cardiac output and ↓stroke volume with exercise. Multivariate predictors of outcome were resting V_{max}, the rate of change in V_{max} (m/s/y), and functional status score; exercise variables did provide additive prognostic information.	No complication in 85%. ↓BP >10 mm Hg in 9%. ST depression >1 mm flat or downsloping in 69%. ST depression >2 mm flat or downsloping persisting >5 m in recovery in 2%.
Amato, 2001(30) 11559673	To determine prognostic value of exercise testing	Prospective	66 Mean age 49.5 y, 67% men	Severe AS (AVA ≤1.0 cm^2)	CAD, arrhythmias, abnormal baseline ECG, comorbid disease	Main outcome measure of sudden death (6%) or symptom onset (52%). Positive ETT in 67%: symptoms in 35%, BP rise <20 mm Hg in 20%, ST changes alone in 12%, ventricular arrhythmia in 7%. Event free survival at 2 y was 19% with a positive ETT and 85% with a negative ETT.	Dizziness during ETT in 12%, no other complications of ETT. The 66 pts were derived from a cohort of 853 consecutive pts. These data may not apply to all AS pts.
Alborino, 2002 (31)	Risk stratification of asymptomatic pts with	Prospective	30 Mean age	Asymptomatic AS	N/A	Abnormal ETT in 18 (60%) with: Fall in BP (3), angina (1), ECG ST changes (3), dyspnea	At 1 y: All 12 pts with a normal ETT

Study	Aim of Study	Study Type	Study Size	Inclusion Criteria	Exclusion Criteria	Exercise Findings/Clinical Outcomes	Comments
12000161	moderate-severe AS		62±14 y			(11)	remained symptom free. 10/18 with abnormal ETT required AVR
Das, 2005 (32) 15820999	Accuracy of stress testing to predict symptom onset at 12 mo	Prospective	125	Asymptomatic AS AVA <1.4 (mean 0.9±0.2) cm^2/m^2 Normal LVEF	Other valve disease. Regional wall motion.	At 1-y follow-up, 36 (29%) developed symptoms. ETT provoked symptoms in 26 (72%) of these pts. Abnormal BP response or ST changes did not improve accuracy of ETT for predicting symptom onset.	Symptoms provoked by ETT had a PPV of 57% and NPV of 87% for onset of symptoms within 1 y. Accuracy was higher in pts under 70 y of age.
Lancellotti, 2005 (33) 16159850	Role of quantitative exercise Doppler	Prospective	69	Asymptomatic AS AVA <1.0 cm^2	Other valve disease, AF, AVR within 2 mo	Abnormal exercise response in 26 (38%) including symptoms, ST depression, failure of BP rise.	Cardiac events (n=18) at 15±7 mo follow-up were predicted by an exercise $\uparrow\Delta P_{mean}$ ≥18 mm Hg, an abnormal exercise test or an AVA <0.75 cm^2.
Marechaux, 2010 (34) 20308041	Assess if exercise hemodynamics provide incremental prognostic value to standard ETT data	Prospective, multicenter	186	Moderate-severe AS Normal LV (LVEF ≥50%)	Symptoms Other valve disease CAD AF/flutter	In the 73% with a normal ETT, 67 had an event (AVR or CV death) at 20±14 mo follow-up. The 27% with an abnormal ETT (symptoms limiting exercise, fall in BP below baseline or complex ventricular arrhythmias) were excluded from analysis.	Adverse events associated with age 65 y, diabetes mellitus, LVH, resting ΔP_{mean} 35 mm Hg, exercise $\uparrow\Delta P_{mean}$ >20 mm Hg.
Rajani, 2010 (35) 11479246	Test if exercise symptoms are due to changes in LV function	Prospective	38	Asymptomatic AVA <1.5 cm^2	N/A	ETT revealed symptom in 10 (26%) which was associated with a lower cardiac index, stroke index, and VO_{2max} compared to those without symptoms.	The only independent predictor of peak cardiac index was the log BNP level (p<0.001; r=0.71)

AF indicates atrial fibrillation, AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular, echo; echocardiography; ECG, electrocardiogram; ETT, exercise treadmill test; LV, left ventricular, LVEF, left ventricular ejection fraction; LVH; left ventricular hypertrophy; MUGA; multi gated acquisition scan; N/A, nonapplicable; NS, nonsignificant; NPV, negative predictive value; NYHA, New York Heart Association; ΔP_{mean}, mean transaortic systolic pressure gradient ; PPV, positive predictive value; pt(s), patients; PVCs, premature ventricular contractions; Q_{max}, maximum flow rate; SEP, systolic ejection period; VO_2max, maximal oxygen consumption.

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Data Supplement 4. Clinical Trials of Lipid Lowering Therapy in Adults With Asymptomatic Mild to Moderate Aortic Stenosis (stage B (Section 3.2.2)

Study Name, First Author, Year	Type of Study, Mean Follow-Up (y)	N	Entry Criteria	Exclusion Criteria	Treatment Group	Serum LDL on Rx (% change from baseline)	Increase in V_{max} (m/s/y) or ΔP_{mean} (mm Hg/y)	Decrease in AVA (cm^2/y)	Other Endpoints	Clinical Endpoints	Study Limitations and Adverse Events
SALTIRE Cowell, 2005 (36) 15944423	Randomized, double-blind, Placebo controlled 2.1 y	134	V_{max} >2.5 m/s Aortic valve Ca^{++} Age >8 y Asymptomatic	Severe MS, AR, or MR LVEF <35% Statin Rx or indication Cholesterol <150 mg/dL Pacer or ICD Child bearing potential Liver disease Alcohol or drug abuse history	Atorvastatin 80 mg/d (n=77)	63±23 mg/dL (↓53%)	V_{max} 0.2±0.21	0.08±0.11	CT valve Ca^{++} ↑22.3±21.0 %/y	Primary endpoints were hemodynamics and valve Ca^{++}	Study drug discontinued in 5% of placebo and 9% of treatment groups. Study not powered for clinical outcomes.
					Placebo (n=78)	130±30 mg/dL (0%)	0.2±0.21 (p=NS)	0.08±0.11 (p=NS)	CT valve Ca^{++} ↑21.7±19.8 %/y		
RAAVE Moura, 2007 (37) 17276178	Open-label, prospective. 1.4 y	121	AVA 1.0–1.5 cm^2 Asymptomatic	CAD, rheumatic mitral valve disease, BAV, liver disease, elevated creatinine, comorbidities	Rosuvastatin 20 mg/d (n=61)	93±21 mg/dL (↓42%)	V_{max} 0.04±0.38	0.05±0.12	Inflammatory markers showed ↓CRP in statin group; ↓IL-6 and ↓sCD4OL in both groups	Endpoints were cholesterol levels and AS severity	Pts with LDL >130 mg/dL at baseline were treated, those with LDL <130 received placebo
					No statin (n=60)	118±29 mg/dL (0%)	0.24±0.30 (p=0.007)	0.1±0.09 (p=0.041)			
ASTRONOMER Chan, 2010 (38) 20048204	Randomized, double-blind, Placebo controlled 3.5 y	269	V_{max} 2.5–4.0 m/s Age 18–82 y Asymptomatic Trileaflet or bicuspid (49%) valve	Clinical indication for statin including CAD, CVD, PVD	Rosuvastatin 40 mg/d (n=134)	1.45 mmol/L (↓54%)	ΔP_{mean} 3.8±4.4	0.08±0.21	7 cardiac deaths 55 AVR	No difference in survival or AVR between groups.	Primary endpoint was AS progression. Composite clinical outcome was secondary outcome.
					Placebo (n=135)	1.61 mmol/L (↑1.8%)	3.9 ±4.9 (p=NS)	0.07±0.15 (p=NS)			
SEAS Rossebø, 2008 (26) 18765433	Randomized, double-blind, Placebo controlled 5.4 y	1,873	V_{max} 2.5–4.0 m/s Age 45–85 y Asymptomatic	CAD, PVD, CVD, DM Clinical indication for statin	Simvastatin 40 mg plus ezetimibe 10 mg/d (n=944)	53±23 mg/dl (↓61%)	V_{max} 0.15±0.01	0.03±0.01	333 composite outcome of CV death, AVR, CHF, and CAD events	No difference for aortic valve related events HR: 1.00; 95% CI: 0.84–1.18	Noncardiac deaths occurred in 5.9% of treatment group and 4.75 of placebo group (p=0.26)
					Placebo (n=929)	139±35 mg/dL (0%)	0.16±0.01 (p=NS)	0.03±0.01 (p=NS)	335 composite outcome (p=NS)		

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BAV, bicuspid aortic valve; CA++, calcium; CAD, coronary artery disease; CHF, congestive heart failure; CI, 95% confidence interval; CRP,C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IL-6; interleukin-6; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; NS, non-significant; ΔP_{mean}, mean transaortic systolic pressure gradient; PVD, peripheral vascular disease; pt(s), patient(s); Rx, prescription; sCD4OL soluble CD40 ligand; Vmax, maximum transvalvular aortic velocity.

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Data Supplement 5. Clinical Outcomes in Asymptomatic Adults With Aortic Stenosis (stages B and C) of Known Hemodynamic Severity (Section 3.2.3)

Author, Year	Study Size (N)	Patient Population Inclusion Criteria	Exclusion Criteria	Pt. Age (y)	% Male	Follow-Up (mo)	AS Severity at Entry	Event-Free Survival	Cardiac Events	Multivariate Predictors of Clinical Outcome
Kelly, 1988 (39) 3337000	51	V_{max} ≥3.5 m/s Asymptomatic	Other valve disease	63±19	75%	17±0	ΔP 68±19 mm Hg	60% at 2 y	21 AS symptom onset 8 deaths (2 cardiac)	N/A
Pellikka, 1990 (40) 2312954	113	V_{max} ≥4.0 m/s Age≥40 y Asymptomatic	Other valve disease CAD Prior valve procedure Early aortic intervention	70 (40–94)	67%	20	V_{max} 4.3 (4–6) m/s	62% at 2 y	37 AS symptoms (20 with AVR) 14 deaths (6 cardiac)	V_{max} ≥4.5 m/s; RR: 4.9 (1.64–14.6) LVEF <50%; RR: 2.93 (0.84–10.2)
Kennedy, 1991 (41) 1991886	66	AVA 0.7–1.2 cm^2 at cath	Other valve disease Previous valve surgery	67±10	77%	35	AVA 0.92±0.13cm^2	59% at 4 y	21 AVR (13 for symptoms) 14 deaths due to AS	LVEF <50%; RR: 1.94 (0.86–4.41). LV-end diastolic pressure >18 mm Hg RR: 2.71 (1.23–5.97). AVA index <0.5 cm^2 RR: 1.93 (0.89–4.23).
Otto, 1997 (21) 9142003	123	V_{max} >2.6 m/s Asymptomatic	Severe comorbid disease	63±16	70%	30	V_{max} <3 m/s V_{max} 3–4 m/s V_{max} >4 m/s	84% at 2 y 66% at 2 y 21% at 2 y	48 AVR for symptoms 8 deaths	V_{max} Functional status score Rate of change in V_{max}
Rosenhek, 2000 (24) 10965007	128	V_{max} ≥4.0 m/s Asymptomatic	Other valve disease	60±18	54%	22±18	V_{max} 5.0±0.7 m/s	67% at 1 y 56% at 2 y 33% at 4 y	59 AVR for symptoms 8 deaths	Extent of valve calcification RR: 4.6 (1.6–14.0).
Rosenhek, 2004 (25) 14972419	176	V_{max} 2.5–3.9 m/s LVEF >50% No AS symptoms	Other valve disease	58±19	59%	48±19	V_{max} 3.1±0.4 m/s	95% at 1 y 75% at 2 y 60% at 5 y	33 AVR for symptoms 34 deaths	Severe valve calcification RR: 2.0 (1.3–3.3). V_{max} ≥3 m/s RR: 1.6 (1.04–2.8). CAD RR: 1.7 (1.2–2.7).
Pellikka, 2005 (42) 15956131	622	V_{max} ≥4.0 m/s No AS symptoms	Other valve disease CAD	72±11	62%	65±48	V_{max} 4.4 ±0.4 m/s	82% at 1 y 67% at 2 y 33% at 5 y	297 AS symptoms (AVR in 207 of these) 103 deaths without AVR or AS symptoms	AVA HR: 0.33 for a 1 cm^2 increase (95%CI: 0.15–0.71). LVH by ECG HR: 1.39 (95% CI: 1.02–1.89).
Rossebo, 2008 (26) 18765433	1,873	V_{max} 2.5 m/s to 4.0 m/s	CAD, CHF, diabetes mellitus, CVA, PVD, and other valve disease	68±9	59%	52 (median)	V_{max} 3.1±0.55	65% at 5 y	668 (36%) Major CV events (death, AVR, CHF, coronary events, and ischemic stroke)	No effect of statin therapy on major CV events.
Lancellotti, 2010 (43) 20483891	163	AVAi ≤0.6 cm^2/m^2 No AS symptoms LVEF ≥55%	Nonsinus rhythm Other valve disease	70±10	65%	20±19	≤0.6 cm^2/m^2	50% at 2 y 44% at 4 y	11 symptoms, but no AVR 57 AVR 6 deaths	V_{max} ≥4.4 m/s, LV longitudinal deformation ≤15.9%, valvulo-arterial impedance ≥4.9 mm Hg/m^2, LA area

Author, Year	Study Size (N)	Patient Population Inclusion Criteria	Exclusion Criteria	Pt. Age (y)	% Male	Follow-Up (mo)	AS Severity at Entry	Event-Free Survival	Cardiac Events	Multivariate Predictors of Clinical Outcome
										≥12.2 cm^2/m^2
Kang, 2010 (44) 20308614	95	AVA 0.75 cm^2 plus V_{max} ≥4.5 m/s or ΔP_{mean} ≥50 mm Hg No AS symptoms	LVEF <50% Other valve disease Age >85 y Malignancy Known CAD	63±12	46%	50	V_{max} 4.9±0.4	71±5% at 2 y 47±5% at 4 y 28±6% at 6 y	18 cardiac deaths 10 noncardiac deaths 46 AVR for symptoms	V_{max} ≥5 m/s age, male sex, EuroScore, degree of valve calcification.
Stewart, 2010 (45) 20513730	183	V_{max} >3 m/s LVEF >50% No AS symptoms	Other valve disease, ACS in previous 6 mo, LVOT obstruction, Respiratory disease, Renal dysfunction	70	65%	31 (median)	AVA 0.81 (IQR: 0.62–1.01) cm^2 V_{max} 3.8 (IQR: 3.3–4.4) m/s	Probability of symptom free survival at 3 y (95% CI) V_{max} <3.5 m/s 0.72 (0.61–0.84). V_{max} 3.5–4.0 m/s 0.46 (0.30–0.62). V_{max} >4.0 m/s 0.32 (0.20–0.44).	103 AS symptoms 3 sudden death	V_{max} HR: 1.43 for each 0.5 m/s increase (95% CI: 1.25–1.64). AVA HR: 1.23 for each -0.1 cm^2 (95% CI: 1.12–1.35).
Rosenhek, 2010 (46) 20026771	116	V_{max} ≥5.0 m/s No AS symptoms	Other valve disease	67±15	49%	41 (median)	V_{max} 5.0–5.5 m/s V_{max} ≥5.5 m/s	43% at 2 y 25% at 2 y	90 AVR 6 cardiac deaths	V_{max}, but not AVA predicted outcome
Jander, 2011 (47) 21321152	435	Low gradient "severe" AS: AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg	CAD, CHF, diabetes, CVA, PVD, and other valve disease (SEAS substudy)	70±9	45%	46±14	V_{max} 3.3±0.5 m/s ΔP_{mean} 26±7 mm Hg AVA 0.82±0.13 cm^2	No difference in event rates between groups	183 AVR 17 HF 34 CV death	Low gradient "severe" AS defined as an AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg was **NOT** a predictor of clinical outcome
	184	Moderate AS: AVA 1–1.5 cm2, ΔP_{mean} 25–40 mmHg		67±9	73%		V_{max} 3.6±0.3 m/s ΔP_{mean} 31±4 mm Hg AVA 1.19±0.13 cm^2		82 AVR 4 HF 9 CV death	
Saito, 2012 (48) 22497679	103	AVA <1.0 cm^2 No AS symptoms	Hx CAD Other valve disease HCM	72±11	45%	36±27	AVAi <0.6 cm^2/m^2 AVAi ≥0.6 cm^2/m^2	41% at 3 y 86% at 3 y	31 AVR 20 cardiac deaths	AVAi <0.6 cm^2/m^2 (HR: 2.6; 95% CI: 11.1–6.3). V_{max} >4.0 m/s (HR: 2.6; 95% CI: 1.2–5.8). (AVA<0.75 cm^2 did not predict outcome) (Mean BSA 1.50±0.15 m^2).

ACS indicates acute coronary syndrome; AS, aortic stenosis; AVA, aortic valve area; AVAi, indexed AVA; AVR, aortic valve replacement; BSA; body surface area; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebral vascular accident; HCM, hypertrophic cardiomyopathy; HF, heart failure; Hx, history; HR, hazard ratio; IQR, interquartile range; LA, left atrium; LV, left ventricular, LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; N/A, not available; ΔP_{mean}, mean transaortic systolic pressure gradient; pt(s), patient(s); PVD, peripheral vascular disease; RR, relative risk; SEAS, Simvastatin Ezetimibe in Aortic Stenosis study; V_{max}, maximum velocity.

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Data Supplement 6. Incidence of Sudden Death in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Section 3.2.3)

First Author	N	Follow-Up (mo)*	V_{max} at Entry (m/s)	AVA at Entry (cm^2)	Sudden Deaths (n)	Sudden Deaths (% per y)
Kelly, 1988 (39) 3337000	51	18	≥3.5	N/A	0	0
Faggiano, 1992 (18) 1626512	37	24	N/A	0.85±015	0	0
Otto, 1997 (21) 9142003	114	30	3.6±0.6	N/A	0	0
Rosenhek, 2000 (24) 10965007	128	22	≥4.0	N/A	1	0.4
Amato, 2001(30) 11559673	66	15	N/A	≤1.0	4	4.8
Das, 2005 (32) 15820999	125	12	N/A	≤1.4	0	0
Pellikka, 2005 (42) 15956131	270	65	≥4.0	N/A	11	0.75
Rossebø, 2008 (26) 18765433	1,873	52	2.5–4.0	N/A	40	0.5
Monin, 2009 (49) 19546391	211	22	≥3.0	≤1.5	2	0.5
Lancellotti, 2010 (43) 20483891	163	20	N/A	≤0.6 cm^2/m^2	3	1.1
Kang, 2010 (44) 20308614	95	59	≥4.5	≥0.75	9	1.9
Marechaux, 2010 (34) 20308041	135	20	N/A	≤1.5	1	0.4
Rosenhek, 2010 (46) 20026771	116	41	≥5.0	N/A	1	0.3
Total	3,384	31*	N/A	N/A	72	0.8

*Mean follow-up duration.
AVA indicates aortic valve area; N/A, not applicable; and V_{max}, maximum aortic velocity
From Rosenhek R et al., (50). (PERMISSION NEEDED)

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Data Supplement 7. Clinical Outcomes in Symptomatic Adults With Aortic Stenosis of Known Hemodynamic Severity (Section 3.2.3)

Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Primary Endpoint	Predictors of Mortality or AVR	Comments
Frank, 1973 (51) 4685905	Outcomes with AS of known hemodynamic severity	Observational	15	Isolated AS. Not referred for AVR Symptomatic (10) or asymptomatic (5) No other valve disease	Mortality from symptom onset: 15% at 2 y 36% at 3 y 52% at 5 y 90% at 10 y	Overlap in hemodynamic parameters between 5 asymptomatic and 10 symptomatic pts	Indexed AVA ranged from 0.26–0.63 cm^2/m^2. Transaortic gradient ranged from 30–90 mm Hg.
Chizner, 1980 (52) 7189084	Outcomes with AS of known hemodynamic severity	Observational	32	Symptomatic AS Not referred for AVR	Mortality from symptom onset: 25% at 1 y 57% by 3 y 64% by 5 y 80% by 8 y	Mortality was no different with "moderate" (AVA 0.71–1.1 cm^2, peak ΔP <70 mm Hg) compared to "severe" AS (AVA 0.7 cm^2, peak ΔP >70 mm Hg).	Time from symptom onset to death: Angina 1.4 (0.25–3.3) y Syncope 0.8 (0.25–2.0) y CHF 2.0 (0.3–3.0) y
Lombard & Selzer, 1987 (53) 3800187	Describe clinical findings in pts with AS of known hemodynamic severity	Retrospective	397	Undergoing cardiac cath for AS Mean age 61 y AVA <1 cm^2 in 87% No other valve disease	Early symptoms (angina and syncope) correlated with AS severity, but not LV function. Late symptoms (HF) correlated with LV dysfunction.	N/A	No outcome data
Turina, 1987 (54) 3609042	Determine prognostic value of hemodynamic and clinical variables	Observational	N/A	Referred for cardiac cath. No AVR due to disease severity or pt refusal	Survival without AVR by AS severity; Severe AS (AVA <0.9 cm^2): 60% at 1 y, 9% at 10 y Moderate AS (AVA 0.95–1.4 cm^2): 97% at 1 y, 35% at 10 y Mild AS (AVA >1.5 cm^2): 85% at 10 y	Survival without AVR by symptom status with severe AS: Symptomatic AS 27% at 2 y 12% at 5 y Asymptomatic AS: 100% at 2 y 75% at 5 y	AS was more severe in severely symptomatic vs. oligosymptomatic pts: ΔP_{mean} 69 vs. 57 mm Hg (p=NS), AVA 0.56 vs. 0.76 cm^2 (<0.01), Cardiac index 2.6 vs. 3.3 L./min/m^2 (p<0.01), LVEDP 17 mm Hg vs.12 mm Hg (p<0.05).
Horstkotte, 1988 (55) 3042404	Compare outcomes with symptomatic vs. asymptomatic severe AS	Retrospective	35	Severe symptomatic AS Refused AVR. AVA 0.4–0.8 cm^2	Mean interval from symptom onset to death: 4.5 y for angina (n=18) 2.6 y for syncope (n=13) <1 y for HF (n=20)	Mortality reached 100% at: 10 y for angina 5 y for syncope 2.4 y for HF	There were 3 sudden deaths before symptom onset
Kelly, 1988 (39) 3337000	Compare outcomes with symptomatic vs. asymptomatic severe AS	Prospective	39	Referred for echo for systolic murmur with Doppler $\Delta P \geq 50$ mm Hg cardiac symptoms, but did not undergo AVR. No other valve disease.	Death in 15 (38%) with a mean follow-up of 12 mo. Compared to 8 (%) deaths in 51 initially asymptomatic pts (See Table 6).	N/A	Study group represents 19% of all surgical candidates for AVR for severe symptomatic AS. Surgery refused by 26/39 pts; symptoms judged not severe in 13 by referring clinician.

Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Primary Endpoint	Predictors of Mortality or AVR	Comments
				Other valve disease.			No difference in Doppler AS severity between these 39 symptomatic and 51 asymptomatic pts during the same time interval.
Otto, 1988 (56) 3143323	Identify echo criteria for AVR with symptomatic AS	Prospective, split sample decision analysis	103	Symptomatic pts undergoing cardiac cath for suspected AS Clinical outcome defined as AVR as determined by clinical cardiologist without knowledge of echo data or death	Decision model recommended AVR in 73 with: V_{max} >4.0 m/s, or V_{max} 3 m/s-4 m/s and AVA<1.0 cm^2 or V_{max} 3 m/s-4 m/s, AVA >1.0 and 2-3+AR	AVR in 68, 2 noncardiac death, 2 nonsurgical candidates, 1 refused	Overall diagnostic accuracy for clinical outcome 94%
					AVR not recommended in 30 with: V_{max} <3.0 m/s or V_{max} 3-4 m/s with AVA ≥1.7 cm^2 or V_{max} 3-4 m/s, AVA 1.1-1.6 cm^2 and 0-1+ AR	No AVR in 28. AVR for severe AR in 2 pts confirmed absence of severe AS by surgical inspection	
Oh, 1988 (57) 3366997	Compare echo and cath data	Prospective	100	Symptomatic AS undergoing cardiac cath	Severe AS at cath defined as (Gorlin AVA ≤0.75 cm^2)	No outcome data	V_{max} >4.5 m/s predicted severe AS at cath with 60% accuracy–specificity 93%, but sensitivity 44% Doppler velocity ratio <0.25 had sensitivity of 92% for severe AS
Galan, 1991 (58) 2018003	Identify echo predictors of AVR	Observational, retrospective	510	Consecutive AS pts undergoing Doppler echo	Comparison with diagnosis of critical AS at cath, defined as Gorlin AVA ≤0.75 cm^2	In 160 pts with V_{max} >4.5 m/s or Doppler AVA ≤0.75 cm^2, 109 underwent AVR No long-term outcome data	V_{max} >4.5 m/s or Doppler AVA ≤0.75 cm^2 was 97% specific for critical AS at cath (n=105) V_{max} ≤4.5 m/s or Doppler AVA >0.75 cm^2 was 95% specific for noncritical AS at cath (n=133)
Otto, 1994 (59) 8313553	Outcomes after aortic balloon dilation	Registry	674	Severe symptomatic AS undergoing aortic balloon dilation V_{max} 4.4±0.8 (2.3–6.6) m/s AVA 0.6 ±0.2 (0.1–1.4) cm^2	Overall survival was 55% at 1 y, 35% at 2 y, and 23% at 3 y, with 70% of deaths classified as cardiac	Multivariate predictors of outcome were functional status, LV systolic function, renal function, sex, cardiac output, and MR	All pts underwent aortic balloon dilation in this registry so outcomes may be worse with no intervention.

AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; cath, catheterization; CHF, congestive heart failure, echo, echocardiography; HF, heart failure; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; MR, mitral regurgitation; N/A, not applicable; NS, nonsignificant; ΔP_{mean}, mean transaortic systolic pressure gradient; pt(s), patient(s); and V_{max}, maximum velocity.

Data Supplement 8. Outcomes in Adults With Low-Flow/Low-Gradient Aortic Stenosis With Preserved Left Ventricular Ejection Fraction (stage S2) (Section 3.2.3)

Study	Aim of Study	Study Type	Study Size	Definition of LFLG severe AS	Exclusion Criteria	Clinical Outcomes	Comments
Hachicha, 2007 (60) 17533183	Determine prevalence, mechanisms and clinical relevant of LFLG severe AS with pLVEF	Retrospective, consecutive pts with severe AS (AVA_i ≤0.6 cm^2 and LVEF ≥50%)	512 pts, mean age 70±14 y, 43% women	181 (35%) LFLG severe AS pLVEF: SV_i ≤35 mL/m^2 **and** AVA_i ≤0.6 cm^2 **and** LVEF≥50% 331 (65%) with normal flow (SV_i >35 mL/m^2) despite AVA_i ≤0.6 cm^2 and LVEF≥ 50%	LVEF <50%	76% survival at 3 y with LFLG severe AS 86% survival at 3 y with normal flow severe AS (p=0.006) Multivariate predictors of overall death were older age, valvulo-arterial impedance ≥5.5 mm Hg/mL/m^2, and medical (vs. surgical) treatment	In LFLG severe AS group: Average BSA 1.8±0.2 m^2 Average AVA 0.76±0.23 cm^2 Average V_{max} 3.5±0.9 m/s LFLG severe AS typically associated with small LV with restrictive physiology
Jander, 2011 (47) 21321152	Evaluate outcome of LG severe AS	Prospective (SEAS substudy)	435 with LG severe AS vs. 184 with moderate AS	AVA <1.0 cm^2 and ΔP_{mean} ≤40 mm Hg (Moderate AS defined as AVA 1.0–1.5 cm^2, ΔP_{mean} 25–40 mm Hg)	See SEAS study in Table 4	Aortic valve events (CV death, AVR,HF due to AS) at 46 mo were no different in pts with LG severe AS vs. those with moderate AS (48.5% vs. 44.6%; p=0.37)	In 223 pts with LFLG severe AS pLVEF (SV_i ≤35 mL/m^2) aortic valve events were no different compared to pts with a normal SVi (46.2% vs. 50.9%; p=0.53).
Tarantini, 2011 (61) 21619977	Investigate outcome after AVR for LFLG severe AS with pLVEF	Retrospective surgical series	73 AVR 29 medical Rx	AVA ≤1.0 cm^2 LVEF >50% ΔP_{mean} ≤30 mm Hg	Age <18 y Other valve disease Previous valve surgery	Overall mortality 37% at mean 42 mo follow-up. Cardiac death in 13 (18%) AVR and 15 (52%) medical Rx pts (p=0.001) AVR was a predictor of survival on multivariate analysis, even in the 78 pts with an AVA between 0.8 and 1.0 cm^2.	Low SVi present in 20 (27%) AVR and 6 (21%) medical Rx pts with no difference in outcome for normal vs. low SVi Retrospective database of 2,055 pts with an AVA ≤1.0 cm^2; LVEF <50% in 25% and LFLG severe AS pLVEF in 5% of pts
Clavel, 2012 (62) 22657269	Compare outcome in AS with normal LVEF with 1) LFLG severe AS, 2) high mean gradient (>40 mm Hg) severe AS, and 3) moderate AS (AVA >1.0 cm^2)	Case match study	187 with LFLG severe AS matched to 187 moderate AS and 187 high-flow severe AS	ΔP_{mean} <40 mm Hg SV_i <35 mL/m^2 and AVA ≤1.0 cm^2	LVEF <50%	Survival at 1 and 5 y: LFLG severe AS pLVEF 89±2% and 64±4% High-gradient severe AS 96±1% and 82±3% Moderate AS 96±1% and 81±3%	AVR associated with improved survival for high-gradient severe AS (HR: 0.18; p=0.001) and LFLG severe AS pLVEF (HR: 0.50; p=0.04), but not for moderate AS
Lancellotti, 2012 (63) 22240128	Evaluate clinical course in AS pts stratified by SVi and ΔP_{mean}	Prospective	150 consecutive pts with asymptomatic severe AS (AVA <1.0 cm^2) referred for ETT	LF: SVi <35 mL/m2 LG: ΔP_{mean} <40 mm Hg (all had AVA <1.0 cm^2)	LVEF <55%, other valve disease, AS, pulmonary disease, inability to exercise	Event free survival at 2 y (p<0.0001): Normal flow (SV_i ≥35 mL/m^2) vs. Low-flow (SV_i <35 mL/m^2) High-gradient ΔP_{mean} ≥40 mm Hg: 44±6% (n=78) vs. 30±12% (n=15) Low-gradient ΔP_{mean} <40 mm Hg: 83±6% (n=46) vs. 27±13% (n=11) Predefined endpoints were CV death in 6 and AVR in 70 pts	

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Study	Aim of Study	Study Type	Study Size	Definition of LFLG severe AS	Exclusion Criteria	Clinical Outcomes	Comments
Herrmann 2013 (15) 23661722	Evaluate outcomes with TAVR compared to medical therapy with LG severe AS	Subgroup analysis of RCT	52 inoperable symptomatic pts with LFLG severe AS with normal LVEF	ΔP_{mean} <40 mm Hg SV_i <35 mL/m^2 and AVA <0.8 cm^2 or AVAi <0.5 cm^2/m^2	LVEF <50%	In 52 inoperable pts with LFLG severe AS with preserved LVEF, 1-y mortality was 66% with TAVR compared to 35% with medical therapy (HR: 0.38; p=0.02). In 87 pts at high risk for surgery, there was no difference between TAVR and SAVR (39.0% vs. 38.3%; HR: 0.91; 95% CI: 0.57–1.45; p=0.69.	
Le Ven 2013 (64) 23770162	Evaluate effect of LV EF and gradient on outcomes after TAVR	Retrospective analysis of registry data	639 severe AS undergoing TAVR	Low flow (SVi <35 mL/m^2) with a normal EF (>50%) was present in 86 (13%) of pts	---	Low flow (but not low EF) was an independent predictor of 30-day mortality (odds ratio: 1.94, p=0.026), cumulative all-cause mortality (hazard ratio: 1.27 per 10 mL/m^2 SVi decrease, p=0.016), and cumulative cardiovascular mortality (hazard ratio: 1.29 per 10 mL/m^2 decrease, p=0.04).	
Mehrotra 2013 (65) 23533186	Compare clinical characteristics and outcomes in AS subgroups	Retrospective echocardiographic database	LFLG severe AS in 38 pts, compared to 75 normal flow low gradient and 70 moderate AS pts.	AVA ≤1.0 cm2 with LVEF≥ 55%, mead gradient <40 mm Hg and SVi <35 mL/m^2.	Mitral valve disease, aortic regurgitation, poor quality study. Severe AS with mean gradient >40 mm Hg.	Survival at 3 years was significantly lower in LF LG compared with NF LG (p=0.006) and moderate AS (p=0.002), but not different between NF LG and moderate AS (p=0.49).	
Ozkan 2013 (66) 23812184	Compare outcomes of LG severe AS with AVR or medical therapy	Prospective follow-up of symptomatic severe LG AS	260 pts with symptomatic severe AS (AVAi ≤0.6 cm^2/m^2) and mean gradient <40 mm Hg	Normal flow present in 125; low flow (SVi ≤35 mL/m^2) in 135.	Mitral disease, aortic regurgitation	At 28 ±24 mos follow-up, 105 pts died (40%): 32 (30%) in the AVR group and 73 (70%) in the medical treatment group. AVR (hazard ratio, 0.54; 95% confidence interval, 0.32–0.94; p<0.001) was independently associated with outcome and remained a strong predictor of survival after adjustment for propensity score. The protective effect of AVR was similar in 125 pts with normal flow (stroke volume index >35 mL/m^2; p=0.22).	
Eleid 2013 (67) 24048203	Evaluate impact of stroke volume with normal EF on outcomes with severe AS	Echocardiographic database.	1,704 consecutive pts with severe AS (AVA <1.0 cm^2) and LVEF≥50%	Low flow = SVi ≤35 mL/m^2 Low gradient <40 mm Hg. LFLG present in 53 pts (3%) compared to normal flow LG (n=352, 21%) and to high gradient severe AS.	Prosthetic valve, congenital or other native valve disease	AVR was associated with a 69% mortality reduction (HR 0.31 (0.25, 0.39) p<0.0001) in LF/LG and NF/HG, with no survival benefit associated with AVR in NF/LG and LF/HG.	

AS indicates aortic stenosis; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; BSA, body surface area; CV, cardiovascular; ETT, exercise treadmill testing; HG, high gradient; HF, heart failure; LFLG, low-flow low-gradient; LF, low-flow; LG, low-gradient; LV, left ventricular; NF, normal flow; pLVEF, preserved left ventricular ejection fraction; ΔP_{mean}, mean transaortic systolic pressure gradient; RCT, randomized controlled clinical trial; Rx, prescription; SEAS, Simvastatin Ezetimibe in Aortic Stenosis study; SVi, stroke volume index; TAVR, transcatheter aortic valve replacement; and $V_{max,}$ maximum velocity.

Data Supplement 9. Choice of Intervention in Symptomatic Adults With Severe Aortic Stenosis (stage D): Surgical Versus Transcatheter Aortic Valve Replacement (Section 3.2.4)

Study	Aim of Study	Study Type	Study Groups (N)	Patient Population	Major Endpoints	Other Results
PARTNER COHORT A (high-surgical risk) (68) 21639811 (69) 22443479	To show that TAVR is not inferior to SAVR	RCT	TAVR 348 vs. SAVR 351 TAVR was transfemoral in 244 and transapical in 104	**Severe symptomatic calcific AS** defined as AVA <0.8 cm^2 plus a mean ΔP ≥40 mm Hg or V_{max} ≥4.0 m/s with NYHA class II-IV symptoms. **High surgical risk** defined as ≥15% risk of death by 30 d after the procedure. An STS score ≥10% was used for guidance with an actual mean STS score of 11.8±3.3% **Exclusions** were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	**All cause death (intention to treat analysis):** **TAVR** / **SAVR** / **p-value** **30 d**: 3.4% / 6.5% / 0.07 **1 y***: 24.2% / 26.8% / 0.44% **2 y**: 33.9% / 35.0% / 0.78 *(p=0.001 for noninferiority) **Composite endpoint at 2 y –all-cause death or stroke**: TAVR 37.1% vs. SAVR 36.4% (p=0.85) HR: 0.93; 95% CI: 0.73–1.18; p=0.55	*Stroke or TIA at 2 y*: TAVR 11.2 % vs. SAVR 6.5 % (p=0.05) *Major vascular complications at 30 d:* TAVR 11.0% vs. SAVR 3.2% (p<0.001) *Major bleeding at 30 d:* TAVR 9.3% vs. SAVR 19.5% (p<0.001) *New-onset AF at 30 d:* TAVR 8.6% vs. SAVR 16.0% (p=0.006).
PARTNER COHORT B (inoperable) (70) 22443478 (71) 20961243	Compare TAVR to medical Rx in inoperable pts with severe symptomatic AS	RCT	TAVR in 179 vs. standard medical therapy in 179 (including BAV in 150 (84%)	**Severe symptomatic calcific AS** defined as AVA <0.8 cm^2 plus a mean ΔP ≥40 mm Hg or V_{max} ≥4.0 m/s with NYHA class II-IV symptoms. **Inoperable** due to coexisting conditions with predicted ≥50% risk of death within 30 d of intervention or a serious irreversible condition. **Exclusions** were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	**All-cause death at 2 y** (Kaplan–Meier): TAVR 43.3% vs. standard therapy 68% HR: with TAVR, 0.58 (95% CI: 0.36–0.92; p=0.02). **Repeat hospitalization:** TAVR 55% vs. 72.5% standard therapy (p<0.001). **Survival benefit of TAVR stratified by STS score:** *STS score <5%* HR: 0.37 (95% CI: 0.13–1.01); p=0.04 *STS score 5%–14.9%* HR: 0.58 (95% CI: 0.41–0.81); p=0.002 *STS score ≥15%* HR: 0.77 (95% CI: 0.46–1.28); p=0.31	**Cardiac symptoms** (NYHA class III or IV) were present in 25.2% of survivors at 1 y after TAVR vs. 58% with standard therapy (p<0.001). **Major stroke** rate at 30 d, was 5.0% with TAVR vs. 1.1% with standard therapy (p=0.06) and remained high at 2 y 13.8% with TAVR vs. 5.5% (p=0.01) **Major vascular complications** occurred in 16.2% with TAVR vs. 1.1% with standard therapy (p<0.001).

AF indicates atrial fibrillation; AMI, acute myocardial infarction; AS, aortic stenosis; AR, aortic regurgitation; AVA, aortic valve area; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; ΔP, mean transaortic pressure gradient; pt(s), patient(s); RCT, randomized controlled trial; Rx, prescription; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; and V_{max}, aortic valve maximum velocity.

Data Supplement 10. Clinical Outcomes of Asymptomatic Patients With Chronic Aortic Regurgitation (Sections 4.3.1.1 and 4.3.3)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Bonow, 1983 (72) 6872164	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled 1973-1982; single institution	77	4.1	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 37 y (range 17–67) Serial echo and radionuclide angiographic studies 63 pts had 3+–4+ AR on aortic root angiography, and the other 14 pts had pulse pressures >70 mm Hg Endpoints: death, symptoms, LV systolic dysfunction	No pt died 12 pts underwent AVR because of symptoms (n=11) or asymptomatic LV dysfunction (n=1) Progression to symptoms or LV dysfunction: less than 4%/y No perioperative deaths in pts who underwent AVR	Percent of pts who did not need surgery was 90±3% (±SE) at 3 y, 81+6% at 5 y, and 75±7% at 7 y. Outcome associated with LVESD, LVEDD, FS, change in LVEF with exercise
Scognomiglio, 1986 (73) 3720042	Determine factors predictive of progression to LV systolic dysfunction	Observational series; single institution	30	4.7	38 initially asymptomatic pts with chronic AR, 30 of whom had normal LV fractional shortening Mean age 26±10 y Serial echo studies Endpoints: death, symptoms, subnormal LV fractional shortening	No pt died Progression to symptoms or LV dysfunction: 2.1%/y Progression to asymptomatic LV dysfunction: 2.1%/y	3 pts developing asymptomatic LV dysfunction had lower initial PAP/ESV ratios and trend toward higher LVESD and LVEDD and lower fractional shortening
Siemienczuk, 1989 (74) 2930091	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV function.	Observational series derived from screening for randomized clinical trial; single institution	50	3.7	Pts included those receiving placebo and medical dropouts in a randomized drug trial of hydralazine therapy; included some pts with NYHA II symptoms. Mean age 48±16 y Serial echo and radionuclide LV angiographic studies	No pt died Progression to symptoms or LV dysfunction: 4.0%/y Progression to asymptomatic LV dysfunction: 0.5%/y	Outcome associated with LVESV, EDV, change in LVEF with exercise, and end-systolic wall stress
Bonow, 1991 (75) 1914102	Determine outcomes of asymptomatic pts with chronic AR; extension of Bonow, 1983	Prospective, observational series; consecutive pts enrolled 1973-1988; single institution	104	8.0	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 37 y (range 17–67) Serial echo (average 7.5 per pt) and radionuclide LV angiographic (average 5.0 per pt) studies Endpoints: death, symptoms, LV systolic dysfunction	2 pts died suddenly Progression to symptoms or LV dysfunction: 2.1%/y Progression to asymptomatic LV dysfunction: 2.1%/y	Outcome associated with age, LVESD, LVEDD, change in LVEF with exercise, and rate of change in LVESD and LVEF at rest with time Initial LVESD >50 mm was associated with risk of death, symptoms, and/or LV dysfunction of 19% per y
Scognomiglio, 1994 (76) 8058074	Effect of nifedipine on outcomes of pts with severe AR and normal LV function	Randomized clinical drug trial (see Data Supplement 11); single institution	74	6.0	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 36±12 y Serial echo studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to death, symptoms or LV dysfunction: 5.7%/y Progression to asymptomatic LV dysfunction: 3.4%/y	This table include only the pts who received digoxin as part of a randomized trial See Data Supplement 11 for outcomes in those receiving active drug (nifedipine, n=69)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Tornos, 1995 (77) 7631617	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1982; single institution	101	4.6	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 41±14 y Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to symptoms or LV dysfunction: 3.0%/y Progression to asymptomatic LV dysfunction: 1.3%/y	Outcome associated with pulse pressure, LVESD, LVEDD, and LVEF at rest Initial LVESD >50 mm was associated with risk of death, symptoms, and/or LV dysfunction of 7% per y
Ishii, 1996 (78) 8759822	Clinical outcome and LV response to chronic AR	Prospective, observational series; consecutive pts 1970-1990; single institution	27	14.2	94 consecutive pts followed for ≥6 mo; the 27 asymptomatic pts with normal LV function are included here Mean age 42±12 y LV function assessed by echo	No pt died Progression to symptoms or LV dysfunction: 3.6%/y	Development of symptoms associated with systolic BP, LVESD, LVEDD, mass index, and wall thickness. LV function not reported in all pts
Borer, 1998 (79) 9494022	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1979; single institution	104	7.3	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 46±15 y 20% of pts in NYHA II initially Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	4 pts died suddenly Progression to symptoms or LV dysfunction: 6.2%/y Progression to asymptomatic LV dysfunction: 0.9%/y	Change in LVEF from rest to exercise, normalized for change in end-systolic stress from rest to exercise was strongest predictor of any endpoint or of sudden cardiac death alone Outcome also associated with initial NYHA II symptoms, change in LVEF with exercise, LVESD, and LVFS
Tarasoutchi, 2003 (80) 12706927	Clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1979; single institution	72	10	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 28±9 y Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to symptoms or LV dysfunction: 4.7%/y Progression to asymptomatic LV dysfunction: 0.1%/y	AR of predominant rheumatic etiology LV function not reported in all pts Development of symptoms associated with LVESD and LVEDD Initial LVESD >50 mm was associated with risk of symptoms and/or LV dysfunction of 7.6%/y
Evangelista, 2005 (81) 16192479	Effect of nifedipine versus enalapril on outcomes of pts with severe AR and normal LV function	Randomized clinical drug trial (see Data Supplement 11); single institution	31	7	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 42±15 y Serial echo studies Endpoints: death, symptoms, LV systolic dysfunction	1 pt died from HF Progression to death, symptoms or LV dysfunction: 3.6%/y	Pts reported here were in the control (placebo) group of this clinical trial See Data Supplement 11 for pts receiving active drugs nifedipine (n=32) and enalapril (n=31)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Detaint, 2008 (82) 19356398	Predictive value of quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution.	251	8	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 60±17 y Serial echo studies to assess severity of AR (ROA and RV) as well as LV dimensions and volumes Endpoints: death, HF, AF, surgery	33 pts died Progression to death or surgery: 5.0%/y Survival at 10 y: Mild AR: 92±4% Moderate AR: 75±6% Severe AR: 69±9% Survival free from AVR at 10 y: Mild AR: 92±4% Moderate AR: 57±6% Severe AR: 20±5%	Surgical indications included symptoms (n=38), LV dysfunction or enlargement (n=17), aortic aneurysm (n=11), IE (n=3, and clinician and/or pt preference [n=11]) Cardiac events (defined as cardiac death, HR, or new onset of AF) associated with RV and ROA as well as ESV index, which superseded M-mode LV dimensions Mortality rate in this series is highest of all series Pts in this series older than all others; only 1 death in pts <50 y in this series
Pizzaro, 2011 (83) 21982316	Predictive value of BNP and quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution	294	3.5	Initially asymptomatic pts with chronic AR and normal LV systolic function The first 160 consecutive pts were analyzed as the derivation set of data (mean age 51±9 y) The next 134 consecutive pts were analyzed as the validation set (mean age 53±10 y) BNP and serial echo studies to assess severity of AR (ROA and RV) as well as LV dimensions and volumes	5 pts died Progression to symptoms or LV dysfunction: 10%/y Progression to asymptomatic LV dysfunction: 2.8%/y	Outcome associated with BNP >130 pg/mL Outcome also associated with RV, ROA, LVESD index, LVEDD index, ESV index, and EDV index
Olsen, 2011 (84) 21414568	Predictive value of speckle-tracking echo in asymptomatic pts with chronic AR and normal LV systolic function	N/A	35	1.6	35 initially asymptomatic pts with chronic AR and normal LV systolic function were followed sequentially Mean age 56±14 y Serial echo studies Endpoints: symptoms, increase in LVEDV >15%, or decrease in LVEF >10% 29 additional pts who underwent AVR at the outset are not reported here	No pts died Progression to death, symptoms, increase in LVEDV or decrease in LVEF: 14.3%/y	Disease progression defined as symptoms, increase in LVEDV >15%, or decrease in LVEF >10% Disease progression associated with reduced myocardial systolic strain, systolic strain rate, and early diastolic strain rate

AF indicates atrial fibrillation; AR, aortic regurgitation; AVR, aortic valve replacement; BNP; brain natriuretic peptide; BP, blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; HF, heart failure; Hx, history; LV, left ventricular; LVEDD, end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic volume; IE, infective endocarditis; N/A, not applicable; NYHA, New York Heart Association; PAP, pulmonary artery pressure; pt(s), patient(s); ROA, regurgitant orifice area; RV, regurgitant volume; and SE, standard error.

2014 Valvular Heart Disease Guideline Data Supplements

Data Supplement 11. Vasodilator Therapy in Asymptomatic Patients With Chronic Aortic Regurgitation (Section 4.3.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints	Results
				Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint & Results*	
Evangelista, 2005 (81) 16192479	Effects of vasodilator therapy on LV function and time to AVR	RCT/95	Intervention: open-label nifedipine-32 pts (20 mg every 12 h) or open label enalapril-32 pts (20 mg every 12 h) vs. Comparator: no treatment-31 pts	Asymptomatic, chronic, severe AR and normal LV function	LVEF <50%., other valve disease. Hypertension, AF, CAD, aortic aneurysm	Open-label nifedipine (20 mg every 12 h) or open-label enalapril (20 mg/d)	No treatment	LVEF Time to AVR	Rate of AVR was similar among the groups: Control group 39% Enalapril group 50% Nifedipine group 41%; p=0.62) No significant group differences in AR severity, LV size or LVEF. Follow-up mean 7 y
Scognomiglio, 1994 (76) 8058074	Assess whether vasodilator therapy reduces or delays the need for AVR	RCT/143	Intervention: Nifedipine (20 mg twice daily)-69 pts vs. Comparator: Digoxin (0.25 mg twice daily)-74 pts	Asymptomatic chronic severe AR with normal LV function	LVEF <50%, recent or worsening AR, hypertension, CAD, AS, other valve disease.	Nifedipine	Digoxin	Time to AVR	AVR in 34%+6% of pts on digoxin versus 15%+3% of pts on nifedipine pts (p<0.001) at 6 y follow-up

AF indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CAD, coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; pts, patients; and, RCT, randomized controlled trial.

2014 Valvular Heart Disease Guideline Data Supplements

Data Supplement 12. Determinants of Outcome After Surgery for Chronic Aortic Regurgitation (Section 4.3.3)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Forman 1980 (85) 7377109	Determinants of survival after AVR	Retrospective, observational series; pts undergoing AVR 1972–1978; single institution	90	3	Indications for AVR not specified; age not specified Preoperative angiography Lillehei-Kastor, Starr Edwards model 2400, and Bjork-Shiley mechanical valves and first generation porcine bioprostheses Endpoint: survival	3-y survival: Overall 79±6% LVEF ≥50% 93±4% LVEF <50% 64±10% p<0.02 CI: ≥2.5 L/m/m^2 93±4% CI: <2.5 L/m/m^2 63±10% p<0.02	High-risk group identified by preoperative angiographic LVEF <50% and/or CI: <2.5 L/m/m^2
Henry 1980 (86) 7353236	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1972–1977; single institution	50	3.7	Indications for AVR; symptoms Mean age 46 y (range 19–68 y) Preoperative echo and hemodynamics Endpoint: survival	4-y survival: Overall 61% LVESD <55 mm 75% LVESD ≥55mm 38% p=0.006	High-risk group identified by preoperative echocardiographic LVFS <25% and/or LVESD >55 mm
Cunha 1980 (87) 7351849	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1973–1977; single institution	86	2.4 (range 1–5.4)	79 symptomatic pts, 7 asymptomatic Mean age 49.6 y (range 17–82 y) Preoperative echo (all pts) and hemodynamics (37 pts) Endpoint: survival	3-y survival: LVFS >35% 100% LVFS 31-35% 91% LVFS ≤30% 78% p<0.05 LVEF ≥60% 100% LVEF <60% 77% p<0.05	High-risk group identified by preoperative echocardiographic LVFS <30%. Mortality also significantly associated with preoperative LVESD. Among pts with FS <30%, mortality higher in NYHA III-IV than in I-II.
Bonow 1980 (88) 6777072	Determinants of survival and LV function after AVR	Prospective, observational series; pts undergoing AVR 1972-1978; single institution	45	3.2	Symptomatic pts undergoing AVR Mean age 44 y (range 20-68 y) Studied with echo, radionuclide LV angiography, and graded treadmill testing Good exercise capacity defined as >stage 1 of NIH protocol Endpoints: survival and LV function	Among 32 pts with subnormal LVFS, those with good vs. poor exercise capacity had: Better survival (100% vs. 47%, p<0.01). Lower postoperative LVEDD (56±8 vs. 68±11 mm, p<0.005) Higher exercise LVEF (5±15 vs. 42±8%, p<0.01)	Exercise capacity imprecise in assessing preoperative LV function in symptomatic pts with AR, but useful in predicting long-term survival after AVR and reversibility of LV dilatation and systolic dysfunction
Borow 1980 (89) 7377221	Determinants of LV function after AVR	Retrospective, observational series; pts undergoing AVR starting 1971; single institution	20	2.0 (range 0.5–5.8)	NYHA: II (20%), III (70%), IV (10%) Preoperative hemodynamics and angiography; postoperative echo Endpoint: LV function (LVFS)	Preoperative LVESVi correlated with postoperative LVFS (r=0.77) The 3 postoperative deaths occurred in pts with preoperative LVESVi 0.60 mL/m^2	In symptomatic pts with AR, preoperative LVESV is an important determinant of postoperative LV systolic function

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Greves 1981 (90) 6451163	Determinants of survival after AVR	Retrospective, observational series; pts undergoing AVR 1973–1979; single institution	42	3.7 (range 0.2–6.6)	38 symptomatic pts, 4 asymptomatic Mean age 45 (range 14–74) Preoperative hemodynamics and angiography Endpoint: survival	5-y survival: Overall 65.3±7.8% (SE) LVEF ≥45% 86.6±6.2% LVEF <45% 53.6±20.1% p=0.04 Cardiac index: ≥2.5L/m/m^2 92±6% Cardiac index: <2.5L/m/m^2 66±16.1% p<0.02	High-risk group identified by preoperative angiographic LVEF <45% and/or cardiac index: <2.5 L/m/m^2 Among pts with LVEF <45%, mortality higher in NYHA III-IV than in I-II.
Kumpuris 1982 (91) 6461239	Determinants of survival, LV function, symptoms after AVR	Prospective, observational series; consecutive pts undergoing AVR 1973–1979; single institution	43	0.67	43 pts with chronic AR and 14 pts with acute AR; only the pts with chronic AR reported here Mean age 46 y (range 18–72 y) Pre- and postoperative echos Endpoint: survival, HF, LV function	Prediction of persistent LV dilatation after AVR (LVEDD >58 mm): Index — Accuracy LVEDD 72 mm — 77% LVESD 50 mm — 86% FS 28% — 70% Mean R/Th 2.5 — 93% MWS 300 mm Hg — 88% ESS 235 mm Hg — 91%	Persistent LV dilatation after AVR predicted by preoperative LVESD, R/Th ratio, mean and end-systolic wall stress; greater precision than LVFS or LVEDD. All deaths occurred in pts with persistent LV dilatation.
Gaasch 1983 (92) 6219153	Determinants of LV function, symptoms after AVR	Prospective, observational series; pts undergoing AVR 1975–1980; single institution	32	Range 1–6	Group A: 25 pts with normal LVEDD after AVR (mean age 45 y, range 18–63 y) Group B: 7 pts with LVEDD >33 mm/m^2 after AVR (mean age 58 y, range 23–74 y) 24 symptomatic pts, 9 asymptomatic (8 in Group A) Pre- and serial postoperative echos Endpoint: symptoms, LV function	Preoperative data, Group A vs. Group B (p<0.001): —LVEDD 69±6 mm vs. 79±6 mm —LVESD 46±7 mm vs. 58±7 mm —LVFS 34±6% vs. 27±6% —R/Th 3.4±0.4 vs. 4.1±0.3 More postoperative symptoms in Group B	Persistent LV dilatation after AVR predicted by echocardiographic LVESD >2.6 cm/m^2 and R/Th ratio >3.8. Trend toward worse survival in Group B (but only 2 deaths in each group at 4 y). Note: Group B was also 12 y older than Group A and more symptomatic.
Fioretti 1983 (93) 6847800	Determinants of LV function after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1972–1980; single institution	47	3.4 (range 0.5–6.3)	All pts symptomatic Group A: 27 pts with LVESD <55 mm (45 y of age, range 22-75 y) Group B: 20 pts with LVESD ≥55 mm (49 y of age, range 22-65 y) NYHA III-IV: Group A 26%, Group B 65% Preoperative echo and angiographic data; postoperative echo at 3 mo and 36 mo Endpoint: LV function	Preoperative data, Group A vs. Group B (p<0.001): —LVEDD 67±7 vs. 82±6 mm —LVFS 33±6 vs. 24±6% —LVEDV 147±43 vs. 247±42 mL/m^2 —LVEF 54±7 vs. 42±9% Postoperative data, Group A vs. Group B: —LVEDD 53±8 vs. 63±7 mm (p<0.001)	Persistent LV dysfunction predicted by preoperative LVEDD ≥75 mm and/or LVESD ≥55 mm. Note greater preoperative symptoms in Group B than Group A

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Stone 1984 (94) 6707364	Determinants of LV function after AVR	Prospective, observational series; consecutive pts undergoing AVR 1962–1977; single institution.	113	4.6±3.3	108 pts symptomatic Mean age 51 y (range 25–77 y) Hemodynamics and angiography in all pts; echo in 44 pts 20 pts with pre- and postoperative echos Endpoint: survival (all pts) and LV function (20 pts)	43 pts died after AVR (8 from HF), no predictors of death Predictors of postoperative LVEDD ≤57 mm: LVESD, LVFS, R/Th ratio Predictors of postoperative LVESD ≤40 mm: LVESD, LVEDD, LV mass	No preoperative variable predicted postoperative LV function. Normal LV size after AVR most likely in pts with preoperative LVFS >26%, LVESD <55 mm, and LVEDD <80 mm
Bonow 1985 (95) 4064269	Determinants of survival and LV function after AVR	Prospective, observational series; consecutive pts undergoing AVR 1976–1983; single institution.	80	3.75 (range 0.5–7.5)	96 consecutive pts; 16 with CAD excluded Group A: 30 pts with normal LVEF Group B: 50 pts with subnormal LVEF Mean age 44 y (range 15–74 y) Preoperative and postoperative echo and radionuclide angiography; preoperative exercise testing Endpoint: Survival, LV function	5 y survival was 83±5%, significantly better than pts undergoing AVR from 1972–1976 (62±9%) Preoperative determinants of postoperative survival: LVEF and FS (both p<0.001) and LVESD (p<0.01) 5 y survival: 96±3% in Group A, 63±12% in Group B (p<0.001)	High-risk group identified by subnormal LVEF at rest. Pts in Group B with poor exercise tolerance and prolonged duration of LV dysfunction were the highest-risk group (5 y survival 52±11) and had greater LVEDD and lower LVEF (both p<0.001) than the others.
Daniel 1985 (96) 3156010	Determinants of survival, symptoms and LV function after AVR	Retrospective, observational series; pts undergoing AVR 1975–1983; single institution.	84	2.5	Consecutive series of pts with high-quality echos Preoperative symptoms not specified Age 46±11 y (range 18–71) Pts with CAD excluded Endpoint: Survival, symptoms, LV function	Survival at 2.5 y: 90.5% in pts with LVFS >25% and LVESD ≤55 mm, but only 70% with LVESD >55 mm and LVFS ≤25%. Survival at 2.5 y: 79% in pts with LVESD >55 mm or LVFS ≤25%.	Outcome after AVR predicted by preoperative LVFS and LVESD. Pts with preoperative LVFS ≤25% had greater postoperative LVEDD compared to those with LVFS >25%: 62±10 vs. 54±7 mm (p<0.05)
Cormier 1986 (97) 3727677	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1968–1983; single institution.	73	4.9±0.8 (range 0.3–14)	All pts in NYHA FC I-II (26 FC I, 47 FC II) Age 46±11 y (range 14–76 y) Echo in 58 pts (LVEDD 70±12 mm; hemodynamics and angiography in 62 pts) (LVEDV 222±55 mL/m^2) Pts with CAD excluded Endpoint: Survival	84% survival at 8 y There were only 2 determinants of survival after AVR: LVEF (p<0.05) and LVESD (p<0.05)	Overall survival good in asymptomatic/mildly symptomatic pts High-risk group identified by preoperative LVEF <40% and LVESD ≥55 mm.
Sheiban 1986 (98) 3727678	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1973–1982; single institution.	84	6.5 (range 3–10)	NYHA: I (12%), II (33%), III (45%), IV (10%) Mean age 42 y (range 20–68) Echo, hemodynamics, and angiography Endpoint: Survival	10-y survival (p<0.01): NYHA I 100%, II 86%, III 70%, IV 0% 5-y survival (p<0.01): —82% in LVESD ≤55 mm; —37% in LVESD <55 mm —81% in LVEF ≥50% ; 62% in LVEF <50%	High-risk group identified by preoperative LVEF <50% and LVESD >55 mm. Severity of preoperative symptoms associated with late survival

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Carabello 1986 (99) 3779916	Determinants of LV function after AVR in pts with preoperative LV dysfunction	Retrospective, observational series; pts undergoing AVR 1980–1987; single institution.	14	1.9±0.67 (range 0.5–6)	Pts with isolated severe AR and LVEF <55% Mean age 49±6 y Pts with CAD excluded Preoperative hemodynamic and echo data; postoperative radionuclide angiography Endpoint: LV function	Preoperative LVESD 57±3 mm Correlation with postoperative LVEF: —LVEDD r=-0.47; p<0.05 —LVEF r=0.55; p<0.05 —R/Th r=-0.56; p<0.05 —LVESV r=-0.62; p<0.05 —LVFS r=0.71; p<0.01 —LVESD r=-0.91; p<0.001	Postoperative LVEF correlated with preoperative LVESD, FS, LVEDD, R/Th ratio Postoperative LVEF most strongly associated with preoperative LVESD
Taniguchi 1987 (100) 3624657	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1978–1985; single institution.	62	3.8±2.2	Age 43±12 y (range 18–64) Group A: LVESV <200 mL/m^2 (n=48), Group B: LVESV >200 mL/m^2 (n=12) Pts with CAD excluded Preoperative hemodynamic and angiographic data Postoperative catheterization in 29 pts Endpoint: Survival and LV function	7-y survival 83±5% Preoperative LVESV index was most important indicator of postoperative death (p<0.001) 6.5 y survival: 92±4% in Group A, 51±16% in Group B (p<0.001) Postoperative data, Group A vs. Group B (p<0.001) —LVEF: 62±7 vs. 42±8% —LVEDV: 98±19 vs. 124±58 mL/m^2	High-risk group identified by preoperative LVESV index >200 mL/m^2 and/or LVEF <40%. No cardiac deaths in Group A
Bonow 1988 (95) 4064269	Factors influencing short- and long-term changes in LV function after AVR	Prospective, observational series; pts undergoing AVR 1976–1983; single institution.	80	Range 3-7	Mean age 43 y (range 19–72 y) Pts with CAD excluded Echo and radionuclide angiography before, 6–8 mo after AVR and 3–7 y after AVR; preoperative exercise testing Endpoint: LV function	Preoperative to early postoperative changes (p<0.001): —LVEDD 75±6 to 56±9 mm —LVEF 43±9 to 51±16% —LVPSS 247±50 to 163±42 dynes/cm^2 Early to late postoperative: no change in LVEDD or PSS, but further increase in LVEF to 56±19% (p<0.001)	Short- and long-term LV function after AVR predicted by preoperative LVEF, FS, LVESD. Among pts with subnormal preoperative LVEF, those with poor exercise tolerance or prolonged duration of LV dysfunction are at highest risk for persistent LV dysfunction
Michel 1995 (101) 8563993	Determinants of long-term survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1994; single institution.	286	6	NYHA: I (19%), II (34%), III (44%), IV (3%) Age 52±13 y (range 17–76 y) Pts with CAD excluded Hemodynamic and echo data Endpoint: Postoperative LV dysfunction defined as clinical HF or LVEF <40% Group A: no postoperative LV dysfunction (n=247); Group B: postoperative LV dysfunction (n=28)	5- and 10-y survival 80% and 60%, respectively Preoperative data, Group A vs. Group B (p<0.001): —LVEF: 48±9 vs. 37±5% —LVFS: 29±7 vs. 21±5% —LVEDD: 69±7 vs. 76±7 mm —LVESD: 49±7 vs. 61±5 mm —NYHA: 44% vs. 82%	Postoperative LV dysfunction predicted by severity of preoperative symptoms and preoperative LVEF, FS, LVESD, LVEDD. On multivariate analysis, preoperative symptoms (p<0.01), LVESD (p<0.03) and LVEF (p<0.04) were significant factors. Determinants of survival not presented.

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Klodas 1996 (102) 8606280	Impact of LV function on survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution	219	5-y and 10-y survival data reported	Group A: preoperative LVEDD <80 mm (n=188, age 55±16 y) Group B: preoperative LVDD ≥80 mm (n=31, age 50±15 y) NYHA III-IV symptoms: Group A 37%, Group B 29% Includes pts with CAD: Group A 37%, Group B 29% Endpoint: Survival	Preoperative data, Group A vs. Group B (p<0.001): —LVEF: 53±11 vs. 43±12% —LVEDD: 67±8 vs. 84±4 mm —LVESD: 45±9 vs. 63±8 mm —LVESS: 96±39 vs. 147±39 dynes x 105/s Postoperative survival, Group A vs. Group B (p=NS): —5 y: 89±3% vs. 87±6% —10 y: 73±5% vs. 71±9% Postoperative survival, LVEF ≥50% vs. <50% (p<0.01): —10 y: 80±5% vs. 63±7%	Extreme LV dilatation associated with LV systolic dysfunction Preoperative LVEF, not degree of LV dilatation, associated with survival
Klodas 1997 (103) 9283535	Impact of symptom severity on survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution	289	5-y and 10-y survival data reported	Group A: NYHA I-II (n=161, age 50±16 y, 86% men) Group B: NYHA III-IV (n=128, age 61±14 y, 70% men) Includes pts with CAD: Group A 11%, Group B 35%; including AVR plus CABG: Group A 8%, Group B 32% (both p<0.0001) Echo data in 249 pts Endpoint: survival	Preoperative data, Group A vs. Group B (p<0.05): —LVEF: 5 3±11 vs. 49±14% 10-y survival, Group A vs. Group B (p<0.001) —Total: 78±7% vs.45±4% —LVEF ≥50%: 82% vs. 40% —LVEF <50%: 73% vs. 40% —Men: 80% vs. 55% —Women: 73% vs. 21% —CAD: 76% vs. 39% —No CAD: 79% vs. 48%	High-risk group identified by symptom severity and preoperative LVEF <50% Survival in Group A equivalent to normal age/sex matched population Note higher frequency of CAD and CABG surgery (and other comorbidities) in the more symptomatic Group B
Turina 1998 (104) 9852889	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1970–1983; single institution	192	18.7 (range 13–26)	Mean age 44 y Endpoint: Survival	Survival rates 76% at 10 y, 55% at 20 y. 83% of long-term survivors in NYHA I-II. Multivariate predictors of late survival: age, LVESV, NYHA, previous IE. LVEF significant in univariate analysis.	High-risk group identified by symptom severity, low LVEF, and elevated ESV.
Chaliki 2002 (105) 12438294	Survival after AVR in pts with normal versus reduced LV function	Retrospective, observational series; consecutive pts undergoing AVR 1980–1995; single institution	450	8.1 (median)	Group A (273 pts, age 56±16) with LVEF ≥50% Group B (134 pts, age 58±15) with LVEF 35%–50% Group C (43 pts, age 58±14) with LVEF <35% LVEF measured by left ventriculography	Operative mortality, Group A vs. B vs. C: 3.7%, 6.7%, 14% (p=0.02) 10-y mortality, Group A vs. B vs. C: 30%, 44%, 59% (p<0.001) 10-y HF rate, Group A vs. B vs. C: 9%, 17%, 25% (p<0.003) Postoperative change in LVEF, Group A vs.	Pts with markedly low LVEF incur have high rates of short- and long-term mortality and HF after AVR. However, postoperative LVEF improves significantly, and most pts survive without recurrence of HF. Thus they should not be denied benefits

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
					and/or echo Endpoint: Survival	B vs. C: -2.3%, 4%, 4.9% (p<0.01)	of AVR.
Tornos 2006 (106) 16516086	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1982–2002; single institution	170	10±6 (range 1–22)	Group A (60 pts age 47±15) mild symptoms (NYHA II), mild LV dysfunction (LVEF 45–50%) or LVESD 50–55 mm Group B (110 pts age 53±14) with NYHA III-IV symptoms or more severe LV dysfunction (LVEF <45% or LVESD >55 mm) Echo data Endpoint: Survival	Cardiac deaths: 5 (9%) in Group A, 28 (28%) in Group B (p=0.002). Survival Group A vs. Group B (p=0.009): 90% vs. 75% at 5 y, 86% vs. 64% at 10 y, 78% vs. 53% at 15 y	Early AVR as defined in the 2006 ACCF/AHA guidelines improves long-term survival in pts with chronic AR. Delaying AVR until more severe symptoms or more severe LV dysfunction decreases postoperative survival.
Bhudia 2007 (107) 17397676	Survival after AVR in pts with marked LV dysfunction compared to normal LV function or mild LV dysfunction	Prospective, observational series; consecutive pts undergoing AVR 1972–1999; single institution	724	8.3±6.5	Group A (88 pts, age 56±12) with severe LV dysfunction (LVEF <30%) Group B (636 pts, age 50±15) with either less severe LV dysfunction or normal LV function Endpoint: Survival	Survival diminished in Group A (severe LV dysfunction) compared to Group B (p=0.04): 81% vs. 92% at 1 y, 68% vs. 81% at 5 y, 46% vs. 62% at 10 y, 26% vs. 41% at 15 y, 12% vs. 24% at 20 y	In propensity matched pts since 1985, these survival trends persisted, but were not significant between pts in Groups A and B (p=0.9): 92% vs. 96% at 1 y, 79% vs. 83% at 5 y, 51% vs. 55% at 10 y

AR indicates aortic regurgitation; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; echo, echocardiography; ESS, end-systolic stress; ESV, end-systolic volume; FS, fractional shortening; HF, heart failure; IE, infective endocarditis; LV, left ventricular; LVEDD, left ejection end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV (i), left ejection end-systolic volume (indexed to body surface area); LVFS, left ventricular fractional shortening; LVPSS, left ventricular peak systolic wall stress; MWS, mean wall stress; NIH, National Institute of Health; NYHA , New York Heart Association; PSS, peak systolic wall stress; pts, patients; and, R/Th, radius to wall thickness ratio.

Data Supplement 13. Hemodynamic Effects Percutaneous Mitral Balloon Commissurotomy (PMBC) Compared to Surgical Closed Commissurotomy (CC) or Open Commissurotomy (OC) (Section 6.2.3)

Author, Year	Mean Follow-Up	Procedure	No. of Patients	Age, y	Average Morphology Score*	Mitral Gradient (mm Hg)		Mitral Valve Area (cm^2)		Restenosis (%)	Freedom From Reintervention (%)	NYHA I (%)
						Pre	Post	Pre	Post			
Patel 1991 (108) 1918709	Immediate	PMBC	23	30±11	6.0	12±4	4±3	0.8±0.3	2.1±0.7†	N/A	N/A	91
		CC	22	26±26	6.0	12±5	6±3	0.7±0.2	1.3±0.3	N/A	N/A	N/A
Turi 1991 (109) 2013139	7 mo	PMBC	20	27±8	7.2	18±4	10±2	0.8±2	1.6±0.2	N/A	N/A	N/A
		CC	20	28±1	8.4	20±6	12±2	0.9±0.4	1.7±0.2	N/A	N/A	N/A
Arora 1993 (110) 8465732	22 mo	PMBC	100	19±5	N/A	N/A	N/A	0.8±0.3	2.3±0.1	5	N/A	N/A
		CC	100	20±6	N/A	N/A	N/A	0.8±0.2	2.1±0.4	4	N/A	N/A
Reyes 1994 (111) 8084354	3 y	PMBC	30	30±9	6.7	N/A	N/A	0.9±0.3	2.4±0.4†	10	N/A	72
		CC	30	31±9	7.0	N/A	N/A	0.9±0.3	1.8±0.4	13	N/A	57
Ben Farhat 1998 (112) 9462525	7 y	PMBC	30	29±12	6.0	N/A	N/A	0.9±0.2	1.8±0.4	N/A	90	87
		OC	30	27±9	6.0	N/A	N/A	0.9±0.2	1.8±0.3	N/A	93	90
		CC	30	28±10	6.0	N/A	N/A	0.9±0.2	1.3±0.3	N/A	50	33
Cotrufo 1999 (113) 10386411	38 mo	PMBC	111	47±14	7.6	N/A	N/A	1.0±0.2	1.8±0.3	28	88	67
	50 mo	OC	82	49±10	8.2	N/A	N/A	1.0±0.2	2.3±0.3	18	96	84

*Wilkins echocardiographic mitral valve morphology score, the sum of a 0 to 4 score for each of 4 characteristics: eaflet mobility, thickness, calcification and chordal involvement .
†Significant difference ($p<0.05$) in increased mitral valve area by PMBC compared with surgical commissurotomy.
CC indicates closed commissurotomy; N/A, not available; NYHA, New York Heart Association; OC, open commissurotomy; Post, postprocedure; PMBC, percutaneous mitral balloon commissurotomy; and, Pre, preprocedure.
Adapted from Bonow et al. (114).
Bhudia SK, McCarthy PM, Kumpati GS, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. J Am Coll Cardiol. 2007;49;1465-71.

Data Supplement 14. Echocardiographic Prediction of Outcome of Percutaneous Balloon Mitral Commissurotomy (Section 6.2.3)

Author, Year	Mean Follow-Up, mo	Echo Criteria	Number of Patients	Age (y±SD)	Survival (%)	Survival Free of Events (%)	Events
Cohen et al., 1992 (115) 1406834	36±20	Score ≤8 Score >8	84 52	N/A	N/A	68% at 5 y 28% at 5 y	Death, MVR, repeat PMBC
Palacios et al., 1995 (116) 7828292	20±12	Score ≤8 Score >8	211 116	48±14 64±11	98% at 4 y 39% at 4 y	98% at 4 y 39% at 4 y	Death, MVR, NYHA III-IV symptoms
Dean et al., 1996 (117) 8917257	38±16	Score ≤8 Score 8–12 Score >12	272 306 24	49±13 58±15 58±15	95% at 4 y 83% at 4 y 24% at 4 y	N/A	Death
Iung et al., 1996 (118) 8557913	32±18	Group 1 Group 2 Group 3	87 311 130	46±13	N/A	89% at 3 y 78% at 3 y 65% at 3 y	Death, MVR, repeat PMBC, FC III-IV symptoms
Cannan et al., 1997 (119) 8996311	22±10	Com Ca- Com Ca+	120 29	N/A	N/A	86% at 3 y 40% at 3 y	Death, MVR, repeat PMBC
Palacios et al., 2002 (120) 11914256	50±44	Score >8 Score <8	278 601	63+14 51+14	82% at 12 y 57% at 12 y	38% at 12 y 22% at 12 y	Death, MVR, repeat PMBC

Echo score based on scoring system of Wilkins et al. (121) mitral valve morphology score, the sum of a 0 to 4 score for each of 4 characteristics: leaflet mobility, thickness, calcification and chordal involvement. Echo groups defined as 1, 2, or 3 based on valve flexibility, chordal fusion and valve calcification (Iung, et al. (112)).

Com Ca indicates commissural calcification; echo, echocardiographic; MVR, mitral valve replacement; N/A, not available; NYHA, New York Heart Association; and, PMBC, percutaneous mitral balloon commissurotomy.

Data Supplement 15. Randomized Trials of Percutaneous Mitral Balloon Commissurotomy Versus Surgery for Mitral Stenosis (Section 6.2.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Results
				Inclusion Criteria	*Exclusion Criteria*			
Patel 1991 (108) 1918709	Compare PMBC by single catheter technique versus CC	RCT/45	Intervention: 23 PMBC vs. comparator: 22 CC	Symptomatic NYHA II or III, tight MS	Mitral valve calcification or left atrial thrombus on 2D echo, more than mild MR or AR, history of systemic embolism within 3 mo of presentation	PBMC	Closed surgical valvotomy	PBMC: MVA increased from 0.8±0.3 cm^2 to 2.1±0.7 cm^2 (p<0.001) CC: MVA increased from 0.7±0.2 cm^2 to 1.3±0.3 cm^2 (p<0.001)
Ben 1998 (112) 9462525	Compare the early invasive and long-term (7 y) clinical and echo follow-up results of PBMC with those of OC and CC for the treatment of tight pliable rheumatic MS	RCT/90	Intervention: PBMC vs. comparator: CC; OC	Rheumatic tight rheumatic mitral valve stenosis (MVA <1.3 cm^2),	Other valve disease, previous thromboembolism, mitral valve calcification, and left atrium thrombus, AF, severe pulmonary hypertension or mild-to-moderate TR	PBMC	CC or OC	Increase in Gorlin MVA : PBMC (from 0.9±0.16 to 2.2±0.4 cm^2), OC (from 0.9±0.2 to 2.2±0.4 cm^2), CC (from 0.9±0.2 to 1.6±0.4 cm^2). Residual MS (MVA <1.5 cm^2): 0% after PBMC or OC and 27% after CC. No early or late mortality or thromboembolism among the 3 groups. At 7-y follow-up, echo MVA was similar and greater after PBMC and OC (1.8±0.4 cm^2) than after CC (1.3±0.3 cm^2; p<0.001). Restenosis (MVA <1.5 cm^2) rate was 6.6% after PBMC or OC vs. 37% after CC. Residual ASD in 2 pts and 3+ MR in 1 pt in the PBMC group. NYHA class I in 87% of pts after PBMC and 90% of pts after OC vs. CC 33% (p<0.0001) Freedom from reintervention 90% after PBMC, 93% after OC, and 50% after CC.
Turi 1991 (109) 2013139	Compare PBMC with surgical CC	RCT/40	Intervention: 20 PBMC vs. Comparator: 20 CC	Pts deemed acceptable as candidates for both procedures	N/A	PBMC	Surgical CC	No differences between groups in pulmonary artery wedge pressures, mitral valve gradients, and MVA at 1 wk and at 8 mo. (all p>0.4).
Arora 1993 (110) 8465732	Compare the immediate and long-term results of PBMC vs. CMC	RCT/200	Intervention: 100 vs. Comparator: 100	Symptomatic pts with moderate-to-severe MS	Pts with more than minimal mitral valve calcification AF, or >2+ MR	PBMC	CC	Both procedures resulted in significant and similar increases in MVA (PBMV: 0.85±0.28 to 2.39±0.94 cm^2; CC: 0.79±0.21 to 2.2±0.85 cm^2; p=NS). MR developed in 14 pts after PBMC and in 12 pts after CC. Restenosis (defined as a loss of >50% of the achieved

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Results
				Inclusion Criteria	*Exclusion Criteria*			
								increase in MVA) was seen in 4 (5%) pts after PBMV and in 3 (4%) after CC.
Reyes 1994 (111) 8084354	Compare PBMC to OC for treatment of rheumatic MS	RCT/60	Intervention: 30 vs. Comparator: 30	Severe rheumatic MS, in sinus rhythm, no severe subvalvular disease/ calcification or more than mild MR	Coexisting other cardiac or valve disease, stroke, severe pulmonary hypertension, low body weight, Lutembacjer's syndrome, and pt decision not to be randomized	PBMC	Open surgical commissurotomy	MVA at 3 years was larger after PBMC (2.4±0.6 cm^2) vs. OC (1.8±0.4 cm^2). NYHA class I at 3 years in 72% or PBMC pts and 57% of OC pts
Cotrufo 1999 (113) 10386411	Compare PPMC vs. OC	RCT/193	Intervention: PBMC 111 vs. Comparator: OC 82	N/A	N/A	PBMC	OC	Survival, event free analysis, recurrent restenosis No hospital mortality in both groups (p=0.3) Hospital complications: 4/111 PBMC vs. 1/82 OC (p=0.3)

2D indicates 2-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; ASD, atrial septal defect; CC, closed commissurotomy; echo, echocardiography; MR, mitral regurgitation, MS, mitral stenosis; MVA, mitral valve area; N/A, not applicable; NS, nonsignificant; NYHA, New York Heart Association; OC, open commissurotomy; PMBC; percutaneous mitral balloon commissurotomy; pts, patients; RCT, randomized controlled trial; and, TR, tricuspid regurgitation.

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Data Supplement 16. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation (Section 7.3.3)

Study, Year	Study Design	Type of Surgery	Number of Patients	Outcome Assessed	Findings
Schuler 1979 (122) 436214	Retrospective	MVR	20	LV function	12 pts with average LVEF 0.70 had normal postoperative LVEF; 4 pts with average LVEF 0.58 had postoperative LVEF 0.25.
Phillips 1981 (123) 7282546	Retrospective	MVR	105	Survival	LVEF <0.50 predicted poor survival.
Zile 1984 (124) 6693615	Prospective	MVR	16	HF, LV function	LVESD index >2.6 cm/m^2 (45 mm) and LVFS <0.32 predicted poor outcome.
Crawford 1990 (125) 2317900	Prospective	MVR	48	Survival, LV function	LVEF <0.50 predicted reduced survival; ESV >50 mL/m^2 predicted persistent LV dilatation.
Wisenbaugh 1994 (126) 8012639	Registry	MVR MVR-CP	26 35	Survival, LV function	LVESD, LVEDD, and FS predicted poor survival and LV function; only LVESD significant in multivariate analysis.
Enriquez-Sarano 1994 (127) 8044955	Retrospective	MVR Repair	214 195	Survival	LVEF <0.60 predicted poor survival whether MVR or CP was preformed; LVEF estimated by echo FS or visual analysis.
Enriquez-Sarano 1994 (128) 7930287	Retrospective	MVR Repair	104 162	LV function	LVEF, LVESD, LV diameter/thickness ratio and end-systolic wall stress predicted outcome; LVEF estimated by echo FS or visual analysis.

CP indicates chordal preservation procedure; ESV, end-systolic volume; FS, fractional shortening; HF, heart failure; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVFS, left ventricular fractional shortening; MVR, mitral valve replacement; PAWP, pulmonary artery wedge pressure; and, pts, patients.

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Data Supplement 17. Primary Mitral Regurgitation—Evidence for Intervention (Section 7.3.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Tribouilloy 1999 (129) 9918527	Assess impact of symptom status on outcome	Retrospective	478	Mitral surgery	NYHA class I,II, III, IV	Advanced preoperative symptoms increased operative mortality by 10 fold. Long-term survival also reduced.
Gillinov 2010 (130) 20667334	Assess impact of symptoms on outcomes	Retrospective propensity-matched	4,253	MVR	NYHA all class	Even NYHA class II preoperative symptoms impaired late survival.
Rosenhek 2006 (131) 16651470	Assess outcome with watchful waiting	Prospective	132	Watchful waiting for severe MR	N/A	Survival for watchful waiting identical to age normal population, but triggers for surgery occurred early after enrollment in 50%.
Kang 2009 (132) 19188506	Assess outcome with watchful waiting	Prospective	447	Mitral surgery	Early surgery vs. watchful waiting	Early surgery appeared superior, but several unoperated pts refused surgery despite presence of triggers.
Enriquez-Sarano 1994 (127) 8044955	Assess predictors of outcome	Retrospective	409	Mitral surgery	LVEF >60, 50-60, <50	Survival at 10 y, 72% for LVEF >60, 53%, 50–60, 32%, <50.
Tribouilloy 2009 (133) 19909877	Assess impact of LVESD on outcome	Retrospective	739	Mitral surgery	LVESD <40 vs. ≥40	LVESD >40 mm nearly doubled late mortality risk.
Enriquez-Sarano 2005 (134) 15745978	Assess impact of MR severity	Prospective	450	N/A	ERO of different sizes	ERO >0.4 cm^2 nearly tripled mortality, but mortality was reduced by surgery.
Ghoreshi 2011 (135) 21962906	Assess impact of pulmonary HTN on outcome	Retrospective	873	Mitral surgery	Preoperative-pulmonary HTN of various degrees	5 y survival 88% for PAP <40 vs. 52% PAP >60.
Goldman 1987 (136) 3624663	Compare LV function after replace vs. repair	Prospective	18	Mitral surgery	Repair vs. replacement	LVEF fell following replacement, but not repair.
David 1984 (137) 6492840	Compare outcome with and without chordal presentation	Prospective	27	Mitral surgery	MV surgery with and without chordal preservation	LVEF decreased without preservation, but was maintained with preservation.
Rozich 1992 (138) 1451243	Examined LVEF	Retrospective	15	Mitral surgery	Chordal preservation vs. destruction	Afterload increased following chordal destruction, but decreases following preservation.
Grigioni 2008 (139) 19356418	Outcome of repair vs. replacement	Prospective	394	Mitral surgery	Repair vs. replacement vs. nonsurgery	92% 54 y survival for repair 80% for replacement.

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Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Gillinov 2008 (140) 18721551	Outcome of repair vs. replacement	Retrospective	328	N/A	Repair vs. replacement propensity	5, 10, 15 y survival 95, 87, 68 repair vs. -80, 60, 44 replacement.

ERO indicates effective regurgitant orifice; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve repair; N/A not applicable; NYHA, New York Heart Association; PAP, pulmonary artery pressure; and, pts, patients.

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Data Supplement 18. Secondary Mitral Regurgitation—Evidence for Intervention (7.4.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Kang 2006 (141) 16820626	Outcome surgery in moderate-to-severe ischemic MR	Retrospective	107	CABG + repair	CABG	Higher operative mortality with CABG and MV repair vs CABG alone (12% vs 2%) but similar 5 year survival (88% vs 87%)
Rossi 2011 (142) 21807656	Impact of SMR on outcome	Retrospective	1,256	None	Impact of SMR on HF	After adjusting for LVEF and other factors-SMR increased mortality by 2-fold
Wu 2005 (143) 15680716	Impact of surgery on moderate-severe MR	Retrospective	126	Surgery with mitral annuloplasty	Med Rx	No survival advantage to mitral valve annuloplasty
Mihaljevic 2007 (144) 17543639	Impact of mitral surgery moderate-severe on SMR	Retrospective	290	CABG+ MV surgery	CABG	1-, 5-, 10-y survival -88, 75, 47 CABG vs. 92, 74, 39 CABG + MV Sx; (p=NS) functional class improved equally in both groups
Benedetto 2009 (145) 19377377	Impact of MV surgery on SMR	Meta-analysis	2,479	CAGB+MV surgery	CABG	No difference in survival or symptomatic status
Fattouch 2009 (146) 19619766	Impact of MV surgery in ischemic MR	Randomized prospective	102	CABG + repair	CABG	No difference in mortality. Repair group had reduced cardiac dimensions and symptoms vs. CABG alone
Deja 2012 (147) 22553307	Impact of repair in ischemic SMR	Randomized to medical Rx vs. surgery	104	CABG + repair	CABG	53% mortality CABG, vs. 43% mortality CABG + MVR (p=NS); after adjustment CABG + MVR had better survival

CABG indicates coronary artery bypass graft; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve, MVR, mitral valve repair; NS, nonsignificant; pts, patients; Rx, prescription; SMR, secondary mitral regurgitation; and, Sx, symptoms.

Data Supplement 19. Functional Tricuspid Regurgitation: Outcomes Following Tricuspid Valve Surgery (Sections 8.2.3 and 8.4.3)

Study, Year	Aim of Study	Study Type	Study Size, Details	Outcomes	Comments, Limitations
Dreyfus, 2005 (148) 15620928	Determine benefit of TV annuloplasty based on intraoperative measurement of TA size	Prospective, observational series 1989–2001; single surgeon	311 pts undergoing MVR for chronic severe MR. 163 pts with TA <70 mm received isolated MVR (Group 1); 148 pts with TA ≥70 mm received MVR + TVR (Group 2). 88% of pts had 0-1+ TR preoperatively. No pts in Group 1 had >2+ TR; 2 pts in Group 2 had 3+ TR.	Postoperative TR grade 2.1±1.0 Group 1 vs. 0.4±0.6 Group 2; (p<0.001). TR severity increased >2 grades in 48% of Group 1 pts vs. 2% of Group 2 pts. Progressive TR occurred independent of residual MR, LVEF, and PA pressures. No differences between groups in 10-y actuarial survival or cardiac event-free survival.	No echo core lab. Time at which postoperative echo obtained not specified. Median y of follow-up not specified. Predictors of worsening TR not reported.
Chan, 2009 (149) 19766809	Determine the effects of TR and TV repair on clinical and TTE outcomes in pts undergoing MV replacement.	Retrospective, observational, single center, 1990–2005	624 pts undergoing MV replacement. 231 with ≥2+TR; 125 received TVR, 106 did not. Mean follow-up 6.8±4.8 y.	TVR was associated with a reduction in TR grade and HF symptoms. No difference in survival between groups. Trend for worsening TR in pts with ≤1+TR but dilated TA.	Study spans 15 y Multiple annuloplasty techniques used. 22% of pts had suture annuloplasty.
Calafiore, 2009 (150) 19231373	Evaluate clinical outcomes of pts undergoing TV annuloplasty for ≥moderate TR at time of MVR for functional MR.	Retrospective, observational, single center, 1988–2003	110 pts with ≥moderate TR undergoing MVR for functional MR. 51 pts underwent TV annuloplasty (treated). 59 pts did not have TV annuloplasty (untreated). Midterm propensity score analysis.	Adjusted 5-y survival was 45.0±6.1% in untreated group and 74.5±5.1% in treated group (p=0.004). Untreated ≥moderate TR a risk factor for lower midterm survival (HR: 2.7; 95% CI: 1.3–5.4) and survival in NYHA class I or II (HR: 1.9; 95% CI: 1.1–3.4). Follow-up functional TR progression rate (3+/4+) was 5% in treated group vs. 40% in untreated group (p<0.001). The progression of functional TR grade at follow-up was a risk factor for worse survival and the possibility to be alive in NYHA class I or II.	Study span 15 y. DeVega annuloplasty in all pts. All pts had functional MR. Incomplete TTE follow-up.
Di Mauro, 2009 (4) (151) 19233670	Evaluate impact of ≥moderate TR on midterm outcomes of pts undergoing surgery for functional MR	Retrospective, observational, single center 1988–2003	165 pts with functional MR and untreated TR 102 pts with 0-1+TR 63 pts with 2-3+TR	5-y survival and NYHA class better for pts with 0-1+TR. Negative impact on survival of untreated moderate or more TR (HR: 3.1; 95% CI: 1.8–5.1; p<0.001). TR grade initially declined after MV surgery, but then progressed in pts with 2-3+ preoperative TR.	Study span 15 y. Incomplete TTE follow-up. No information on success of MV surgery. Same pt cohort as reported by Calafiore 2009.
Van de Veire, 2011 (152) 20832082	Determine if TV annuloplasty in pts with TA dilatation undergoing MVR prevents progression of TR and RV remodeling	Retrospective, observational, single center series, 2 separate cohorts: 2002 and 2004	2002: 13 pts with 3-4+ TR underwent TV annuloplasty at time of MVR 2004: 21 pts with 3-4+TR and 43 pts with TA ≥40 mm underwent TV annuloplasty at time of MVR	2002 cohort: no evidence of RV reverse remodeling; TR grade unchanged. For 23 pts without 3-4+ TR but with TA dilatation, TR grade worse and RV size larger at 2 y. 2004 cohort: RV reverse remodeling with reduction in TR grade in 43 pts with TA dilatation who underwent TV annuloplasty.	Limited clinical data. Reason for choice of these 2 observational pt cohorts not provided.
Yilmaz, 2011 (153) 21277597	Examine clinical and TTE outcomes of pts with "clinically silent" TR undergoing isolated MVR for prolapse	Retrospective, observational, single center, 1995–2006	n=699 pts with MVP Preoperative TR grade was 1-2+ in ≥80% of pts. Pts with right HF or primary TR excluded.	Overall TR grade decreased significantly at 1 y. Independent risk factors for worsening TR included female sex, preoperative AF, diabetes mellitus. In pts with <moderate preoperative TR (mean grade, 1.6 [0.49]), mean TR grade remained stable and increased only slightly after 5-y follow-up (mean, 2.0 [0.86]; p<0.01).	TA measurements not provided. All pts had MVP. Other, but not all investigators have reported that the incidence of TR after MVR may be dependent on the etiology of

Study, Year	Aim of Study	Study Type	Study Size, Details	Outcomes	Comments, Limitations
				In pts with at least moderate preoperative TR, mean TR grade decreased significantly from preoperative values after MVR (p<0.001 at hospital discharge, <1 y, and 1–3 y). Mean TR grade trended down at 3 and 5 y after surgery (p=0.18 after 3 y; p=0.33 after 5 y). Degree of preoperative TR was not associated with early or late mortality.	MR. Effect of recurrent TR on survival not reported.
Calafiore, 2011 (154) 21163499	Determine benefit of TV annuloplasty for TR based on TA diameter	Retrospective, observational, single center 2006–2008	298 pts with ≥1+ TR undergoing MV surgery. 167 underwent TVR, 108 with ≥moderate TR and 59 with TA >24 mm. 137 did not have TVR, 16 with ≥moderate TR and 81 with TA >24 mm.	In pts who did not undergo TVR, TA >24 mm was a risk factor for increasing TR grade during follow-up (HR: 2.4; 95% CI: 1.4–5.1; p=0.020).	DeVega annuloplasty used in all pts with TA <28 mm. Small cohort sizes.
Navia, 2012 (155) 22093694	Identify factors associated with TVR; assess safety and efficacy of TVR	Retrospective, observational, single center series 1997–2008	91(5%) of 1,724 pts with 2+ TR undergoing left-sided heart valve surgery. Propensity analysis performed for 91 matched pairs. Pts nonrandomly selected for TVR had more severe indices of RV remodeling with TV tethering.	In propensity-matched groups, prevalence of early postoperative TR grades 0 and 1 was 83% after TVR vs. 46% in the no-repair group 11% of the repair group had persistent grade 2+ TR after TVR, compared with 39% of the no-repair group. Worse TR on was present in 7% of the TVR group, vs. 15% of the no-repair group (p<0.0001). Differences in TR grade for matched pts were sustained at over 3 y. TVR did not add significant in-hospital morbidity or mortality. Long-term survival of propensity matched pts did not differ.	Multiple TVR techniques used Limited long-term outcome and TTE data. Matched pairs differed significantly.
Kim, 2012 (156) 21930721	Assess clinical and TTE outcomes of TVR in pts with mild-to-moderate TR at time of MV replacement	Retrospective, observational, single center, 1997-2008	236 pts with mild-moderate TR undergoing mechanical MV replacement for rheumatic disease. 123 pts underwent TVR. 113 pts did not undergo TVR.	Freedom from moderate-severe TR at 5 y 92.9±2.9% in repair group vs. 60.8+/16.9% in nonrepair group (p<0.001). Approximately 10% of pts with mild TR who did not have repair progressed to ≥moderate TR over 10 y. No differences between groups in mortality, need for TV reoperation, or HF. Postoperative moderate-severe TR an independent predictor of poorer event-free survival (HR: 2.90; p=0.038).	All pts had rheumatic MV disease. Groups significantly unbalanced at baseline. Limited TTE follow-up information, especially regarding MV prosthesis function, PA pressures, etc.
Benedetto 2012 (157) 22244561	Determine if TV annuloplasty in pts with TA dilatation and ≤moderate TR prevents TR progression after MV surgery	Randomized, prospective, single institution, 2008-2009	44 pts undergoing MV surgery with ≤2+ TR and TA ≥40 mm on preoperative TTE. Randomized 1:1 to TV annuloplasty with a flexible ring or no TV annuloplasty. Primary endpoint: ≥3+ TR at 1 y.	≥3+ TR at 1 y 0% in TV annuloplasty group vs. 28% in no annuloplasty group (p=0.02). Compared with no annuloplasty, TV annuloplasty resulted in significant RV reverse remodeling. Distance during 6-min walk test greater in the TV annuloplasty group (p=0.008).	Small sample size. Nonblinded endpoint assessment.

AF indicates atrial fibrillation; echo, echocardiography; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVP, mitral valve prolapse; MVR, mitral valve repair; NYHA, New York Heart Association; PA, pulmonary artery; pt(s), patients; RV, right ventricle; TA, tricuspid annulus; TR, tricuspid regurgitation; TTE, transthoracic echocardiography TV, tricuspid valve; and, TVR, tricuspid valve repair.

Data Supplement 20. Clinical Outcomes With Bioprosthetic and Mechanical Valves (Section 11.1.2)

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
Hammermeister 2000 (158) 11028464	575 pts undergoing isolated AVR (394) or MVR (181) at 13 VA medical centers (1977–1982)	RCT	Isolated AVR or MVR. Concurrent CABG performed in 39% of AVR and 36% of MVR pts.	Women, contraindications to VKA anticoagulation, requirement for antiplatelet therapy, valve size ≤19 mm AVR or ≤25 mm MVR, active endocarditis.	15 y	AVR, all-cause mortality at 15 y was lower for MHV vs. BHV: (66±3% [mean±SE] vs. 79±3%; p=0.02) No difference for MVR. Primary valve failure was significantly greater with a BHV vs. MHV valve, both for AVR (23±5% vs. 0±0%; p=0.0001) and MVR (44±8% vs. 5±4%; p=0.0002). Primary valve failure nearly always (93%) occurred in pts <65 y. AVR reoperation was higher after BHV vs. MHV (29±5% vs. 10±3%; p=0.004). No statistically significant difference for MVR.	Pts receiving mechanical MVR were older and had more hypertension than those with a bioprosthetic MVR.
Oxenham, 2003 (159) 12807838	541 pts undergoing MVR (261), AVR (211), or both (61) 1975–1979	RCT	Mean age 53.9 (10.6) y. 56% female.	Additional valve procedures or not eligible for VKA anticoagulation.	20 y	No difference in overall survival (Bjork-Shiley vs. porcine prosthesis [mean (SEM]): 25.0 (2.7)% vs. 22.6 (2.7)%, log rank test p=0.39. Combined endpoint of death and reoperation occurred in 23.5 (2.6)% with BHV vs. 6.7 (1.6)% with MHV (log rank test; p<0.0001). Major bleeding was more common in pts with MHV (40.7 [5.4]% vs. 27.9 [8.4]% after 20 y; p=0.008), with no significant difference in major embolism or endocarditis.	Older generation valve types.
Stassano 2009 (160) 19892237	310 pts undergoing AVR 1995–2003	RCT	Age 55–70 y	Other valve surgery. Contraindication to VKA anticoagulation	Mean 106±28 mo	No survival difference at 13 y between BHV and MHV groups. Valve failures and reoperations were more frequent in the BHV group compared with the MHV group (p=0.0001 and p=0.0003, respectively). No differences in the linearized rate of thromboembolism, bleeding, endocarditis, and MAPE between the MHV and BHV valve groups.	Power may not be adequate to detect a clinically meaningful difference at longer follow-up.
Khan 2001 (161) 11479498	Initial AVR in 1389 pts, MVR in 915 pts, 1976–2001 at	Retrospective, observational	Age 64.5±12.9 y for MHV Age 72.0±12.6 y for BHV	Homografts, combined MHV and BHV procedure, any previous	20 y	Freedom from reoperation at 15 y for AVR was 67±4.8% for BHV and 99±0.5% for MVH. For MVR, freedom from reoperation was 52±5.7% for BHV and 93±3.2% for MHV.	Not prospective, not randomized. Concurrent CABG in

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
	a single medical center.			valve surgery		Survival at 15 y (BHV vs. MHV, p=NS for all): AVR in pts <65 y (55±5.9 vs. 61±5.3%), AVR in pts >65 y (17±3.4 vs. 17±3.8%). MVR in pts <65 y (32±5.5 vs. 51±5.4%), MVR in pts >65 y (12±3.5 vs. 18±3.8%)	50%.
Chan 2006 (162) 16733156	3,063 pts undergoing AVR 1982–1998	Retrospective, observational	2,195 BHV and 980 MHV.	Previous cardiac surgery	Average follow-ups in y for the BHV and MHV groups were 7.5±4.7% and 5.9±3.3% (p<0.001), respectively	Valve-related mortality (per pt-y): BHV 1.0% vs. MHV 0.7% Valve-related reoperation (per pt-y): BHV 1.3% vs. MHV 0.3% (p<0.001) Valve-related morbidity: BHV 0.4% vs. MHV 2.1% (p<0.001) Actual freedom from valve-related reoperation favored MHV for pts <60 y. Actual freedom from valve-related morbidity favored BHV for pts >40 y. Actual freedom from valve-related mortality was similar for BHV vs. MHV >50 y.	Not randomized. AVR only. Concomitant CABG in 43.5% of BHV pts and 26.0% of MHV pts.
Kulik 2006 (163) 16857373	659 pts age 50–65 y with initial AVR or MVR	Prospective, observational	AVR in 388 (MHV 306, BHV 48). MVR in 236 (MHV 188, BHV 48).	Enrolled only if survived perioperative period. Valve repair excluded.	Mean 5.1±4.1 y; maximum 18.3 y	Freedom from primary endpoint MAPE at 10 y (reoperation, endocarditis, major bleeding, or thromboembolism): AVR MHV 70±4.1% vs. BHV 41.0±30.3% (p=0.55) MVR MHV 53.3±8.8% vs. BHV 61.2±9.2% (p=0.34) Multivariate analysis did not identify valve type as an independent risk factor for MAPE	Not randomized. Surgeon choice of valve type. Concurrent CABG in 29%.
Ruel 2007 (164) 17846320	567 pts undergoing AVR or MVR	Retrospective, observational	Age <60 y. First heart valve operation.	N/A	Mean survivor follow-up, 24.0±3.1 y	Survival in AVR: no difference between BHV vs. MHV (HR:0.95, 95% CI: 0.7–1.3); Survival in MVR: no difference between BHV or MHV (HR: 0.9, 95% CI: 0.5–1.4); Long-term survival worse in MVR than AVR (HR: 1.4, 95% CI: 1.1–1.8); Reoperation in 89% of BHV AVR and 84% of BHV MVR (older generation devices) with reoperative mortality 4.3%.	Not randomized or prospective, follow-up available in only 23% of original cohort.
van Geldorp 2009 (165) 19327512	Bioprosthetic AVR=2,860 (73%) vs. mechanical AVR=1,074 (27%)	Retrospective cohort (1982–2003) Microsimulation used to calculate age-specific pt	Bioprosthetic AVR: mean age=70 y, mean follow-up=6.1 y, CABG=47% vs. Mechanical AVR: mean age=58 y, mean follow-up=8.5 y, CABG=28%	N/A	Bioprosthetic AVR: mean follow-up=6.1 y. Mechanical AVR: mean follow-up=8.5 y.	Simulated events for a 60-y man undergoing AVR, favors a BP vs. MP: • life-expectancy: 11.9 vs. 12.2 y, • event-free survival: 9.8 vs. 9.3 y, • reoperation-free: 10.5 vs. 11.9 y, • reoperation risk: 25% vs. 3%,	Methodology of microsimulation is dependent on quality of dataset, wide chronological age of prostheses.

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
		outcome after AVR				• risk of bleeding: 12% vs. 41%	
Badhwar 2012 (166) 22364968	172 pts undergoing isolated AVR or MVR (2003–2007)	Prospective, nonrandomized, matched pairs for BP vs. MP	Mean age 56.2±9.6 y (range, 24–72 y).	Limited 5 y survival based on comorbidity	Median follow-up 4.0 y	At a median 4-y follow-up, thromboembolism was 0.77% for MP and 0.78% for BP (p=NS) There was a survival benefit of mechanical prostheses at 7.5 y. Noninferiority to bioprosthetic AVR for bleeding and thromboembolic complications.	Prosthesis choice by surgeon, not randomized. Low INR targets (AVR: 2.0, MVR: 2.5) with home monitoring point-of-care system
Weber 2012 (167) 22341653	206 pts undergoing AVR (2000–2009)	Retrospective, with propensity matching of 103 BP to 103 MP AVR	Age <60 y. AVR with or without concurrent CABG, aortic root surgery, mitral or tricuspid valve repair.	Additional valve replacement.	Median follow-up 33±24 mo (2–120 mo)	Overall survival was worse with BP (90.3% vs. MP=98%, p=0.038; HR:0.243, 0.054–0.923 Freedom from valve related complication complications was similar: BP=54.5% vs. MP=51.6%, p=NS	Concurrent CABG in 49.9%, 14% were reoperations

AVR indicates aortic valve replacement; BHV, bioprosthetic heart valve; CABG, coronary artery bypass graft; HTN, hypertension; INR, international normalized ratio; MAPE, major adverse prosthesis-related events; MHV, mechanical heart valve; MVR, mitral valve replacement; N/A, not applicable; NS, nonsignificant; RCT, randomized controlled trial; pts, patients; VA, Veterans Affairs; and, VKA, vitamin K antagonist.

Data Supplement 21. Bridging Anticoagulation Therapy for Mechanical Heart Valves (Section 11.3.2)

Author, Year	Study Type	Patient Population		Study Size and Comparator (N)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Hammerstingl 2007 (168) 17578050	Prospective, observational	Pts with MHV undergoing major surgery (n=25) or minor surgery (n=36), pacer implantation (n=21), or cardiac cath (n=34)	N/A	116 pts: MVR 31) , AVR (76) or DVR (9) Bridging with enoxaparin in all (renal function dose adjusted)	No thromboembolic (95% CI: 0–3.1%) complications. 1 major bleeding complication (0.86%; 95% CI: 0.02–4.7%). Minor bleeding in 10 pts (8.6%; 95% CI: 4.2–15.3%) at a mean of 5.4±1.4 d LMWH therapy.	Not randomized, no comparison group, relatively small study group.
Spyropoulos 2008 (169) 18805116	Observational, prospective, multicenter registry in USA, Canada	Adults undergoing elective surgery or invasive procedure with a mechanical valve on long-term VKA	Enrolled in another bridging study within 30 d.	73 with IV UFH (1,535±532 U/h) vs. 172 with SQ LMWH (76% enoxaparin 1 mg/kg bid, 13% dalteparin 100 U/kg bid, 4% tinzaparin 175 U/kg/d)	Major adverse event rates (5.5% vs. 10.3%; p=0.23) and major bleeds (4.2% vs. 8.8%; p=0.17) were similar in the LMWH and UFH groups, respectively; 1 arterial thromboembolic event occurred in each group. More LMWH-bridged pts were treated as outpts or discharged from the hospital in <24 hours (68.6% vs. 6.8%; p <0.0001). Multivariate logistic analysis found no significant differences in major bleeds and major composite adverse events when adjusting for cardiothoracic or major surgery between groups.	Not randomized, bridging therapy chosen by clinician. The LMWH group was less likely to undergo major surgery (33.7% vs. 58.9%; p=0.0002) and cardiothoracic surgery (7.6% vs. 19.2%; p=0.008), and to receive intraprocedural anticoagulants or thrombolytics (4.1% vs. 13.7%; p=0.007)
Pengo 2009 (170) 19470892	Prospective inception cohort at 22 Italian centers, 2005–2007	Adults undergoing surgical or invasive procedures that required interruption of long-term VKA therapy	Body weight <40 kg. Creatinine >2.0 mg/dL, contraindication to LMWH, need for dual antiplatelet Rx	N=189 MHV valve pts (15% of total study size of 1,262). Bridging with 70 anti-Xa U/kg/bid for high-risk pts.	Intention-to-treat analysis for the entire study population: Thromboembolic events in 5 pts (0.4%; 95% CI: 0.1–0.9), all in high-thromboembolic-risk pts Major bleeding in 15 (1.2%; 95% CI: 0.7–2.0) and minor bleeding in 53 pts (4.2%; 95% CI: 3.2–5.5). Major bleeding was associated with twice-daily LMWH (high-risk pts), but not with the bleeding risk of the procedure.	Only 15% had mechanical valves, no comparison group. Safety in pts with MHV valves has not been conclusively established

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Author, Year	Study Type	Patient Population		Study Size and Comparator (N)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Daniels 2009 (171) 19232682	Retrospective cohort, 1997–2003	MHV on chronic VKA therapy undergoing invasive procedures or surgery	N/A	A total of 580 procedures: 372 AVR, 136 MVR and 48 multivalvular. UFH or LMWH bridging used in high-risk pts (older AVR, any MVR, additional risk factors for TE). No bridging in isolated AVR pts.	**Events at 3 mo N (%)** / **No Heparin N=213** / **LMWH Only N=243** / **Any UFH N=99** Thromboembolism 1 (0.5) / 2 (0.8) / 2 (3.1) Major Bleeding 5 (2.4) / 9 (3.7) / 6 (6.1) Minor Bleeding 13 (6.1) / 13 (5.4) / 8 (8.1) Overall cumulative incidence of TE at 3 mo was 0.9%; all events occurred within 1 wk of the procedure. No TE events in 93 pts with isolated AVR with no bridging.	Not randomized, choice of therapy individualized based on estimated TE and bleeding risk. Most frequent procedures were GI endoscopy (19.1%), urologic procedures (14.0%), angiography or transcatheter interventions (10.5%), and orthopedic surgery (10.3%).
Bui HT 2009 (172) 19892063	Retrospective cohort study	173 pts on VKA anticoagulation for MHV (n=90) or for nonvalvular AF undergoing invasive or surgical procedures	Age <18 y, Pregnancy, Hypercoagulable condition, bioprosthetic valve	130 bridging episodes with LMWH were used to compare outcomes in MHV vs. pts with AF.	No deaths or thromboembolic events at 2 mo. Major and minor bleeding rates were similar between the MHV and AF groups (3.2% and 2.9%, 14.5% and 13.2% respectively, p=NS).	Isolated AVR in 43 (48%) of mechanical valve pts. Not randomized. Comparator group of AF may not require bridging. No sample size calculation for power of study.
Biteker 2012 (173) 22591673	Prospective cohort, single center	Consecutive pts undergoing noncardiac surgery	Bioprosthetic valves, severe liver or renal disease, contraindication to heparin	140 pts with MHV (77 AVR, 46 MVR, and 17 DVR) receiving enoxaparin 1 mg/kg bid compared to 1,200 pts with native valves (control group) receiving no anticoagulation.	**Events (3 mo) N (%)** / **MHV with LMWH N=140** / **Native valves N=1200** / **p-value** Bleeding 18.6% / 14.2% / NS Thromboembolism 3.6% / 2% / NS Mortality 1.4% / 1.3% / NS Cardiovascular events 10.8% / 10.7% / NS	Not randomized. Comparison group did not have valve disease. No power calculation with small number of MHV pts.
Weiss 2013 (174) 23648452	Retrospective, single-center cohort study	Consecutive pts requiring postoperative bridging therapy after cardiac surgery during a 19 mo period	N/A	N=402 receiving LMWH (enoxaparin): comparison of full-dose (FD=1 mg/kg bodyweight bid) to half-dose (HD=0.5 mg/kg bid) with renal function dose adjustment.	**Events (by hospital discharge) N (%)** / **Full dose LMWH N=210** / **Low dose LVWH N=210** / **p-value** Mortality 0.5% / 5.5% / 0.003 Thromboembolism 5% / 9% / 0.277 Bleeding 11% / 5% / 0.126 Hospital stay (d) 15.1±9.3 / 12.5±8.1 / 0.003	Not randomized, but well matched (first half of cohort received FD, second half HD) Included only 100 (25.9% of total) pts with MHV, also included AF in 83.6%.

AF indicates atrial fibrillation; AVR, aortic valve replacement; DVR, double-valve replacement; FD, dull dose; GI, gastrointestinal; HD, half dose; LMWH, low molecular weight heparin; MHV, mechanical heart valve; MVR, mitral valve replacement; N/A, not available; NS, nonsignificant; pt(s), patient(s); TE, thromboembolism; UFH, unfractionated heparin; USA, United States of America; and, VKA, vitamin K antagonist.

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Data Supplement 22. Fibrinolytic Therapy for Prosthetic Valve Thrombosis (Section 11.6.2)

Author, Year	Study Type	Patient Population		Intervention vs. Comparator (n)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Deviri 1991 (175) 1993782	Observational, single center, surgical treatment for PVT, 1980–1989	n=100 (32 male) aged 5 mo–82 y (median 32 y) with PVT (n=61) or pannus (n=7), or both (n=44)	N/A	Only included pts undergoing surgery for PVT or pannus. AVR in 51 (48%), MVR in 49 (46%), and both in 6 (6%)	Early mortality 12.3% (n=13) Perioperative mortality higher in pts with NYHA IV (17.5%) vs. NYHA I-III (4.7%) symptoms, p<0.05 Same outcome between valve replacement vs. declotting	Older generation mechanical PHV, chart-recovered data, various diagnostic approaches.
Tong 2004 (176) 14715187	International registry of pts with suspected PVT, 1985–2001	107 pts (71 females; age 24 to 86 y) from 14 centers (6 in the U.S.) MVR=79, AVR=13, TVR=15	N/A	Only included pts with suspected PVT who underwent TEE and were treated with FT	Hemodynamic success rate 85% Overall complications rate 17.8% Death in 5.6% Independent predictors of complications: 1) thrombus area >0.8cm^2 (OR: 2.41 per cm^2, CI: 1.12–5.19) and 2) Hx of stroke (OR: 4.55, CI: 1.35–15.380) Presentation with shock was associated with clinical failure 10.7% vs. 0%; p=0.0032	Not all pts had PHV obstruction, thrombolysis criteria not standardized. Goal of study was to assess role of TEE measurement of thrombus burden.
Roudaut 2009 (177) 19427604	Observational, nonrandomized single center over 20 y, 1978–2001	n=263 episodes in 210 pts (98% left sided valves)	Decision for surgical vs. FT made by each clinician.	Surgery=136 Fibrinolysis=127	**Outcomes** / **Surgery N=136** / **FT N=127** / **p-value ….** Restored valve fx: 89% / 70.9% / <0.001 Mortality (6 y): 26% / 48% / 0.002 Thromboembolism: 0.7% / 15% / <0.001 Major Comp.: 11.1% / 25.2% / 0.05 Recurrent PVT: 11% / 25% / 0.021	Not randomized (standard clinical practice). Use of FT decreased over study interval. Older generation valves.
Karthikeyan 2009 (178) 19738134	Randomized, controlled, single Indian center	120 pts with first episode of left sided PVT	Contraindications to FT, symptom duration >2 wk, recurrent PVT	Accelerated infusion of streptokinase vs. conventional infusion	Complete clinical response: Accelerated=38/59 (64.4%) vs. Conventional=32/60 (53.3%), HR: 1.6, 95% CI: 0.9-2.5, p=0.055. Overall success rate 59%, with lower success rate (24%) in pts with NYHA III/IV symptoms. Composite secondary outcome (death, major bleeding, embolic stroke, systemic TE): HR: 1.4%,95% CI: 0.5–3.5; p=0.50 Major bleeding: HR: 2.2, 95% CI: 0.6–7.7, p=0.24	No surgical comparison group. Low success rate with both types of therapy.
Keuleers 2011	Retrospective,	n=31 PVT:	Contraindications	Surgery (n=18) compared	Surgery: 2 (11%) perioperative deaths,	Small numbers, no data on

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Author, Year	Study Type	Patient Population		Intervention vs. Comparator (n)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
(179) 21211605	nonrandomized, single center, 1988–2008	MVR=17 (55%), AVR=8 (26%), TVR=6 (19%).	to FT	to FT (n=13)	2 (11%) recurrent PVT (follow-up 76 mo) FT: 8 (61%) with restoration of normal valve function. 4 (31%) recurrent PVT (follow-up 18 mo) 4 (31%) major complications (death, stroke, TIA, or bleeding requiring surgery)	thrombus size
Özkan 2013 (66) 23489534	Observational , single center clinical experience, 1993–2009	TEE-guided FT in 182 consecutive pts with 220 episodes of PVT in 220 different episodes (156 women; mean age, 43.2±13.06 y).	Contraindications to FT, asymptomatic PVT with normal valve hemodynamics and no TE or with, thrombus size <10 mm.	FT regimen adjusted over study duration with Groups: **I**–Slow streptokinase **II**–Rapid streptokinase **III**–tPA 100 mg (bolus) **IV**–tPA 50 mg 6 h infusion **V**–tPA 25 mg 6 h infusion	**Outcomes** / **I** / **II** / **III** / **IV** / **V** / **p-value** **N**: 16 / 41 / 12 / 27 / 124 Overall success: 68.8% / 85.4% / 75% / 81.5% / 85.5% / 0.46 Major nonfatal comp.: 12.5% / 12.2% / 8.3% / 11.1% / 4.8% / NS Death: 12.5% / 2.4% / 16.7% / 3.7% / 0% / 0.01 Multivariate predictors of mortality plus major nonfatal complications: Any thrombolytic therapy regimen other than Group V and a history of stroke/TIA.	
Karthikeyan 2013 (180) 23329151	Meta-analysis	Published articles on left-sided PVT with at least 5 pts each treated with surgery and FT	Lack of data on primary outcome (restoration of normal valve function)	7 studies with 690 episodes of left sided PVT, 446 treated with surgery, and 244 with FT.	**Outcomes** / **Surgery** N=446 / **FT** N=244 / **OR** / **p-value** Restored valve Fx: 86.5% / 69.7% / 2.53, 95% CI: 0.94–6.78 / 0.066 Death: 13.5% / 9% / 1.95, 95% CI: 0.63–5.98 / 0.244 Thromboembolism: 1.6% / 16% / 0.10, 95% CI: 0.04–0.24 / <0.001 Major Bleeding: 1.4% / 5% / 0.27, 95% CI: 0.08–0.98 / 0.046 Recurrent PVT: 7.1% / 25.4% / 0.25, 95% CI: 0.08–0.74 / 0.013	

AVR indicates aortic valve replacement; FT, fibrinolytic therapy; fx, function; Hx, history; MVR, mitral valve replacement, N/A, not available; NS, nonsignificant; NYHA, New York Heart Association; PHV, prosthetic heart valves; pts, patients; PVT, prosthetic valve thrombosis; TE, thromboembolism, TEE, transesophageal echocardiography; TIA, transient ischemic attack (stroke); TVR, tricuspid valve replacement; and, U.S., United States.

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Data Supplement 23. Paravalvular Regurgitation (Section 11.8.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events
				Inclusion/Exclusion Criteria	Primary Endpoint & Results	Secondary Endpoint & Results	
Orszulak 1983 (181) 6860002	To report outcome with surgical reoperation for PVR	Retrospective N=105	Surgical reoperative repair of prosthetic PVR	Aortic PVR (n=75) and mitral PVR (n=29)	Early mortality for entire cohort: 5.7%. 5-y survival was 94% for aortic PVR pts and 75% for mitral PVR pts.	21 pts required multiple operations for persistent PVR. 85% of survivors at follow-up up to 14 y were NYHA I or II. Murmur of residual or recurrent PVR evident in 21% of pts.	N/A
Miller 1995 (182) 8556176	To identify clinical features that predict occurrence of PVR. Outcome after surgical repair also reported	Retrospective N=30	Surgical reoperative repair of aortic prosthetic PVR	Aortic prosthetic PVR	30-d survival=90%; 5-d survival=73%	Prosthesis replacement in 26, suture repair in 4. Trivial or no residual regurgitation in 16 of 20 with echocardiography in follow-up.	N/A
Akins 2005 (183) 16359061	To examine acute and long-term outcome of surgery for PVR	Retrospective N=136	Surgical reoperative repair of aortic or mitral prosthetic PVR	Mitral PVR in 68% Aortic PVR in 32%	Operative mortality, 6.6% Perioperative stroke, 5.1% 10-y survival, 30%	Primary repair in 48%, prosthesis replacement in 52%	N/A
Pate 2006 (184) 16969856	To describe outcome in series of pts undergoing percutaneous repair of PVR	Retrospective N=10 (10 defects)	Percutaneous repair of PVR	Mitral PVR (n=9) and aortic PVR (n=1); 9 were not surgical candidates	7 with successful procedure 3 pts died at 1 y	4 of 10 required second procedure 6 with sustained improvement in symptoms	1 retroperitoneal bleed 1 device dislodgement
Shapira 2007 (185) 11479246	To examine the feasibility and early outcome of percutaneous repair of PVR	Retrospective N=11 (13 defects)	Percutaneous repair of PVR	Mitral PVR (n=8), aortic PVR (n=1), and both aortic and mitral PVR (n=2) Estimated surgical mortality, 17.8%	10 with device deployment 6 with reduction in regurgitation 5 with NYHA improvement by 1 class	Hemolysis improved in 4, worsened in 4, and was unchanged in 2 in early follow-up 3 deaths in follow-up	N/A
Cortes 2008 (186) 18237605	To examine utility of TEE in percutaneous repair of PVR	Retrospective N=27 (27 defects)	TEE before and procedure (n=27) and at follow-up ≥1 mo (n=17)	Mechanical mitral PVR in pts at high risk for surgery	62% with procedure success TEE helped guide procedure and identified variety of complications	N/A	2 stroke 1 cardiac perforation 6 needing blood transfusion for postprocedural anemia
Ruiz 2011 (187) 22078427	To examine feasibility and efficacy of the percutaneous repair of PVR	Retrospective/ N=43 (57 defects)	Percutaneous repair of PVR	Mitral PVR (n=36), aortic PVR (n=9), and both aortic and mitral PVR (n=2)	Device deployment success in 86% of pts and 86% of leaks Survival: 92% at 6 m, 86% at 18 m	12 pts required multiple procedures Reduction in need for transfusions or EPO from 56–5% NYHA class improved by ≥1 in 28/35 pts	2 device embolizations 1 emergency surgery 1 vascular complication 1 procedural death
Sorajja 2011	To examine the feasibility and	Retrospective	Percutaneous repair of	78% mitral PVR, 22% aortic	Device deployment in 89%	Leaflet impingement in 4.3%	30-d events

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events
				Inclusion/Exclusion Criteria	Primary Endpoint & Results	Secondary Endpoint & Results	
(188) 21791673	early outcome of percutaneous repair of PVR	N=115 pts (141 defects)	PVR	PVR Average STS risk score=6.9%	Mild or no residual regurgitation in 77% No procedural death	Procedure time average 147 min and decreased with case experience	Death, 1.7% Stroke, 2.6% Emergency surgery, 0.9%, Bleeding=5.2%
Sorajja 2011 (189) 22078428	To determine the long-term clinical efficacy of percutaneous repair of PVR	Retrospective N=126 (154 defects)	Percutaneous repair of PVR	79% mitral PVR, 21% aortic PVR Average STS risk score=6.7%	3-y survival, 64% HF accounted to 37% of deaths; noncardiac cause in 30%	Symptom improvement occurred only in pts with mild or no residual regurgitation Hemolytic anemia persisted in 14 of 29 pts	Survival free of death or need for cardiac surgery was 54% at 3 y Need for cardiac surgery related to degree of residual regurgitation

EPO indicates erythropoietin; HF, heart failure; N/A, not applicable; NYHA, New York Heart Association; pts, patients; PVR, paravalvular regurgitation; STS, Society of Thoracic Surgeons; and, TEE, transesophageal echocardiography.

Data Supplement 24. Surgical Outcome in Infective Endocarditis (Section 12)

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Jault, 1997 (190) 9205176	Identify significant predictors of operative mortality, reoperation, and recurrent IEs	Retrospective single-center surgical cohort study	247	NVE alone; surgery 100%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (n=19). Overall survival rate (operative mortality excluded) was 71.3% at 9 y. The probability of freedom from reoperation (operative mortality included) was 73.3±4.2% at 8 y. The rate of IE of the implanted prosthetic valve was 7%.	Increased age, cardiogenic shock at the time of operation, insidious illness, and greater thoracic ratio (>0.5) were the predominant risk factors for operative mortality; the length of antibiotic therapy appeared to have no influence. Increased age, preoperative neurologic complications, cardiogenic shock at the time of operation, shorter duration of the illness, insidious illness before the operation, and mitral valve endocarditis were the predominant risk factors for late mortality. Risk factors for reoperation were younger age and aortic valve endocarditis.
Castillo, 2000 (191) 10768901	To determine the clinical features and long-term prognosis of IE in pts who were not drug users.	Prospective single-center case series	138	NVE 69%, PVE 31%; surgery 51%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Severe complications (HF, embolic phenomenon, severe valve dysfunction, abscesses, renal failure, and immunologic phenomenon) occurred in 83% of pts. 51% of pts underwent surgery during the active phase (22% was emergency surgery) Inpt mortality was 21%. Overall 10 y survival was 71%	There were no significant differences in survival depending on the type of treatment received during the hospital stay (medical vs. combined medical-surgical) in this observational study.
Alexiou, 2000 (192) 10881821	Single center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late outcome	Retrospective single-center surgical cohort study	118	NVE 70%, PVE 30%; 100% of pts underwent surgery	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (9 pts). Endocarditis recurred in 8 (6.7%). A reoperation was required in 12 (10.2%). There were 24 late deaths, 17 of them cardiac. Actuarial freedom from recurrent endocarditis, reoperation, late cardiac death, and long-term survival at 10 y were 85.9%, 87.2%, 85.2%, and 73.1%, respectively.	Predictors of operative mortality: HF, impaired LV function. Predictors of recurrence: PVE. Predictors of late mortality: myocardial invasion, reoperation. Predictors of poor long-term survival: coagulase-negative staphylococcus, annular abscess, long ICU stay.
Wallace, 2002 (193) 12067945	To identify clinical markers available within the first 48 h of admission that are associated with poor outcome in IE	Retrospective single-center cohort study	208	NVE 68%, PVE 32%; surgery 52%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Mortality at discharge was 18% and at 6 mo 27%. Surgery was performed in 107 (51%) pts. In-hospital mortality was not influenced by surgery (23% vs. 15% in the nonsurgical group); p=0.3 At 6 mo there was a trend towards increased mortality in the surgical group (33% vs. 20%)	Duration of illness, age, gender, site of infection, organism, and LV function did not predict outcome. Abnormal white cell count, raised creatinine, ≥2 major Duke criteria, or visible vegetation conferred poor prognosis.
Hasbun, 2003 (194)	To derive and externally validate a prognostic	Retrospective multicenter cohort study	513	Pts with left-sided NVE with current	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease,	In the derivation and validation cohorts, the 6-mo mortality rates were 25% and 26%, respectively. In the derivation cohort, pts were classified into 4	5 baseline features were independently associated with 6 mo mortality (comorbidity [p=0.03], abnormal mental status [p=0.02], moderate-to-severe congestive HF

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
12697795	classification system for pts with complicated left-sided native valve IE			indication of surgery in 45%`	symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings	groups with increasing risk for 6-mo mortality: 5%, 15%, 31%, and 59% (p<0.001). In the validation cohort, a similar risk among the 4 groups was observed: 7%, 19%, 32%, and 69% (p<0.001).	[p=0.01], bacterial etiology other than viridans streptococci [p<0.001 except *S. aureus*, p=0.004], and medical therapy without valve surgery [p=0.002])
Vikram, 2003 (195) 14693873	To determine whether valve surgery is associated with reduced mortality in pts with complicated, left-sided native valve IE	Retrospective multicenter cohort study; Propensity analysis	513	Pts with left sided NVE with current surgical intervention in 45%	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, ECG, echocardiography, type of surgery performed, and operative findings	After adjustment for baseline variables associated with mortality (including hospital site, comorbidity, HF, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection), valve surgery remained associated with reduced mortality (adjusted HR: 0.35; 95% CI: 0.23–0.54; p<0.02). In further analyses of 218 pts matched by propensity scores, valve surgery remained associated with reduced mortality (15% vs. 28%; HR: 0.45; 95% CI: 0.23–0.86; p=0.01). After additional adjustment for variables that contribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR: 0.40; 95% CI: 0.18-0.91; p=0.03). In this propensity-matched group, pts with moderate-to-severe congestive HF showed the greatest reduction in mortality with valve surgery (14% vs. 51%; HR: 0.22; 95% CI: 0.09–0.53; p=0.001).	Pts with moderate-to-severe HF showed the greatest reduction in mortality with valve surgery. Stratifying the data by congestive HF among propensity-matched pts undergoing surgery revealed that among pts with none to mild HF, valve surgery was not associated with reduced mortality compared with medical therapy (HR: 1.04; 95% CI: 0.43–2.48; p=0.93). Among propensity-matched pts with moderate-to-severe HF, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR: 0.22; 95% CI: 0.08–0.53; p=0.01).
Habib, 2005 (196) 15958370	To identify prognostic markers in 104 pts with PVE and the effects of a medical versus surgical strategy outcome in PVE	Retrospective multicenter cohort study	104	100% PVE pts; surgery 49%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Overall, 22 (21%) died in hospital. By multivariate analysis, severe HF (OR: 5.5) and *S. aureus* infection (OR: 6.1) were the only independent predictors of in-hospital death. Among 82 in-hospital survivors, 21 (26%) died during a 32 mo follow-up. Mortality was not significantly different between surgical and nonsurgical pts (17% vs. 25%, respectively, not significant). Both in-hospital and long-term mortality were reduced by a surgical approach in high-risk subgroups of pts with staphylococcal PVE and complicated PVE.	Factors associated with in-hospital death were severe comorbidity (6% of survivors vs. 41% of those who died; p=0.05), renal failure (28% vs.45%, p=0.05), moderate-to-severe regurgitation (22% vs. 54%; p=0.006), staphylococcal infection (16% vs. 54%; p=0.001), severe HF (22% vs. 64%; p=0.001), and occurrence of any complication (60% vs. 90%; p=0.05).
Revilla,	Describe the profile	Prospective	508	NVE 66%,	Brucella, Q fever, Legionella, and	Of these 508 episodes, 132 (34%) were electively	Univariate analysis identified renal failure, septic shock,

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
2007 (197) 17032690	of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality	multicenter cohort study		PVE 34%; surgery studied for the present report	Mycoplasma. Persistent infection despite appropriate antibiotic treatment (31%).	operated on, and 89 pts required urgent surgery (defined as prior to completion of antibiotic course). Primary reasons for urgent surgery in these 89 pts were HF that did not respond to medication (72%) and persistent infection despite appropriate antibiotic treatment (31%). 32 pts (36%) died during their hospital stay. 32% of NVE died vs. 45% of pts with PVE. Late PVE was associated with a higher mortality than early PVE (53% vs. 36%)	Gram-negative bacteria, persistent infection, and surgery for persistent infection as factors associated with mortality. Multivariate analysis confirmed only persistent infection and renal insufficiency as factors independently associated with a poor prognosis.
Hill, 2007 (198) 17158121	Analyze epidemiology, optimal treatment, and predictors of 6-mo mortality in IE	Prospective single-center cohort study	193	NVE 66%, PVE 34%; surgery 63%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	43% included staphylococci, 26% streptococci, and 17% enterococci. At least 1 complication occurred in 79% of the episodes and 63% had surgical intervention. 6-mo mortality was 22%: 33% for staphylococci, 24% for enterococci, and 8% for streptococci. 74% of pts with a contraindication to surgery died when compared with 7% with medical treatment without a contraindication and 16% with surgical treatment.	*S. aureus*, contraindication to surgery (present in 50% of deaths).
Remadi, 2007 (199) 17383330	To evaluate the predictors of outcome and to establish whether early surgery is associated with reduced mortality	Prospective multicenter cohort study	116	*S. aureus* IE alone; NVE 83%, PVE 17%; surgery 47%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Antibiotic treatment.	The in-hospital mortality rate was 26%, and the 36-mo survival rate was 57% Surgical group mortality was 16% vs. 34% in the medically treated group ($p<0.05$) In unadjusted analyses, early surgery performed in 47% of pts was associated with lower in-hospital mortality (16% vs. 34%; $p=0.034$) and with better 36-mo survival (77% vs. 39%; $p<0.001$).	Multivariate analyses identified comorbidity index, HF, severe sepsis, prosthetic valve IE, and major neurologic events as predictors of in-hospital mortality Severe sepsis and comorbidity index were predictors of overall mortality After adjustment of baseline variables related to mortality, early surgery remained associated with reduced overall mortality.
Aksoy, 2007 (200) 17205442	To better understand the impact of surgery on the long-term survival of pts with IE	Prospective single-center cohort study with propensity score matching	426	NVE 69%, PVE 19%, "other" 12%; surgery in 29%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Pts' propensities for surgery	The fit of the propensity model to the data was assessed using the concordance index with pts who underwent surgery matched to those who did not undergo surgery, using individual propensity scores. The following factors were statistically associated with surgical therapy: age, transfer from an outside hospital, evidence of IE on physical examination, the presence of infection with staphylococci, HF, intracardiac abscess, and hemodialysis without a chronic catheter.	Revealed that surgery was associated with decreased mortality (HR: 0.27; 95% CI: 0.13–0.55). A history of diabetes mellitus (HR: 4.81; 95% CI: 2.41–9.62), the presence of chronic intravenous catheters at the beginning of the episode (HR: 2.65; 95% CI: 1.31–5.33), and with increased mortality.
Tleyjeh,	To examined the	Matched	546	NVE alone;	Propensity score to undergo valve	Death occurred in 99 of the 417 pts (23.7%) in the	After adjustment for early (operative) mortality, surgery

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
2007 (201) 17372170	association between valve surgery and all-cause 6 mo mortality among pts with left-sided IE	propensity analysis		surgery 24%	surgery was used to match pts in the surgical and nonsurgical groups. To adjust for survivor bias, the follow-up time was matched so that each pt in the nonsurgical group survived at least as long as the time to surgery in the respective surgically-treated pt. Valve surgery was used as a time-dependent covariate in different Cox models.	nonsurgical group vs. 35 deaths among the 129 pts (27.1%) in the surgical group. 18 of 35 (51%) pts in the surgical group died within 7 d of valve surgery.	was not associated with a survival benefit (adjusted HR: 0.92; 95% CI: 0.48–1.76).
Tleyjeh, 2008 (202) 18308866	To examine the association between the timing of valve surgery after IE diagnosis and 6-mo mortality among pts with left-sided IE	Retrospective single-center cohort propensity analysis	546	NVE alone; surgery 24%	The association between time from IE diagnosis to surgery and all-cause 6 mo mortality was assessed using Cox proportional hazards modeling after adjusting for the propensity score (to undergo surgery 0–11 d vs. 11 d, median time, after IE diagnosis).	The median time between IE diagnosis and surgery was 11 d (range 1–30). Using Cox proportional hazards modeling, propensity score and longer time to surgery (in d) were associated with unadjusted HRs of (1.15, 95% CI: 1.04–1.28, per 0.10 unit change; p=0.009) and (0.93; 95% CI: 0.88–0.99, per d; p=0.03), respectively. In multivariate analysis, a longer time to surgery was associated with an adjusted HR (0.97; 95% CI: 0.90–1.03). The propensity score and time from diagnosis to surgery had a correlation coefficient of r=20.63, making multicollinearity an issue in the multivariable model.	On univariate analysis, a longer time to surgery showed a significant protective effect for the outcome of mortality. After adjusting for the propensity to undergo surgery early versus late, a longer time to surgery was no longer significant, but remained in the protective direction.
Thuny, 2009 (203) 19329497	To determine whether the timing of surgery could influence mortality and morbidity in pts with complicated IE	Retrospective single-center cohort propensity analysis	291	NVE 82%, PVE 18%; surgery 100%	The time between the beginning of the appropriate antimicrobial therapy and surgery was used as a continuous variable and as a categorical variable with a cut-off of 7 d to assess the impact of timing of surgery. 2 groups of pts were formed according to the timing of surgery: the "≤1st wk surgery group" and the ">1st wk surgery group". The impact of the timing of surgery on 6 mo mortality, relapses, and PVD was analyzed using PS analyses.	1st wk surgery was associated with a trend of decrease in 6-mo mortality in the quintile of pts with the most likelihood of undergoing this early surgical management (quintile 5: 11% vs. 33%, OR: 0.18, 95% CI: 0.04 –0.83; p=0.03). Pts of this subgroup were younger, were more likely to have *S. aureus* infections, congestive HF, and larger vegetations. ≤1st wk surgery was associated with an increased number of relapses or PVD (16% vs. 4%, adjusted OR: 2.9, 95% CI: 0.99–8.40; p=0.05).	Very early surgery (<7 d) associated with improved survival (especially in highest risk pts), but greater likelihood of relapse or post-operative valve dysfunction.
Manne, 2012 (204)	Describe the morbidity and mortality associated	Retrospective single-center surgical	428	NVE 58%, PVE 42%; surgery 100%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography	Overall 90% of pts survived to hospital discharge. When compared with pts with NVE, pts with PVE had significantly higher 30-d mortality (13% vs. 5.6%;	Pts with IE caused by *S. aureus* had significantly higher hospital mortality (15% vs. 8.4%; p<0.05), 6 mo mortality (23% vs. 15%; p=0.05), and 1 y mortality (28%

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
22206953	with surgery for IE and compare differences in characteristics, pathogens, and outcomes for pts with NVE and PVE from a large surgery-minded tertiary referral center	cohort study			data, and treatment strategy	p<0.01), but long-term survival was not significantly different (35% vs. 29%; p=0.19).	vs. 18%; p=0.02) compared with non–*S. aureus* IE.
Kang, 2012 (205) 22738096	To compare clinical outcomes of early surgery and conventional treatment in pts with IE	Prospective randomized trial at 2 centers with intention to treat analysis	76	Left-side NVE and high risk of embolism to early surgery (49%) vs. conventional treatment (51%)	Pts were randomly assigned in a 1:1 ratio to the early-surgery group or the conventional-treatment group with the use of a Web-based interactive response system. The protocol specified that pts who were assigned to the early-surgery group should undergo surgery within 48 h after randomization. Pts assigned to the conventional-treatment group were treated according to the AHA guidelines, and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted after the completion of antibiotic therapy.	The primary endpoint (composite of in-hospital death and embolic events that occurred within 6 wk after randomization) occurred in 1 pt (3%) in the early surgery group as compared with 9 (23%) in the conventional-treatment group (HR: 0.10; 95% CI: 0.01 –0.82; p=0.03). There was no significant difference in all-cause mortality at 6 mo in the early-surgery and conventional-treatment groups (3% and 5%, respectively; HR: 0.51; 95% CI: 0.05–5.66; p=0.59). The rate of the composite en point of death from any cause, embolic events, or recurrence of IE at 6 mo was 3% in the early-surgery group and 28% in the conventional-treatment group (HR: 0.08; 95% CI: 0.01–0.65; p=0.02).	As compared with conventional treatment, early surgery in pts with IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

AHA indicates American Heart Association; HF, heart failure; ICU, intensive care unit, IE, infective endocarditis; NVE, native valve endocarditis; pts, patients; PVE, prosthetic valve; and *S. aureus,* Staphylococcus aureus.
Table modified from Prendergast BD and Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010, 121:1141-1152.

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Data Supplement 25.Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated with Warfarin or Unfractionated Heparin (UFH) (Section 13.3.2)

Author, Year	Study Aim	Study Size (N)	Patient Population	Study Type	Type of Anticoagulation	Endpoints		Summary	Study Limitations
						Maternal	*Fetal*		
Chan, 2000 (206) 10647757	Systematic review anticoagulation mechanical valves	1,234 pregnancies in 976 women	All pts with mechanical prosthesis–40 articles–treated with differing anticoagulation regimens 1966–1997	Systematic review of literature	1. Warfarin throughout 2. UFH 1st trimester, then warfarin 3. UFH throughout pregnancy 4. No AC	Maternal Death 1. 1.8% 2. 4.2% 3. 15% 4. 4.7% Thromboembolic 1. 3.9% 2. 9.2% 3. 33% 4. 24%	Fetal anomalies 1. 6.4% 2. 3.4% 3. 0% 4. 3.3% Fetal wastage 1. 33% 2. 26% 3. 43% 4. 20%	Reduction of thromboembolic events for mother greatest with warfarin throughout pregnancy, worse maternal outcome with heparin throughout pregnancy. Heparin in 1st trimester reduces risk of fetopathic effects, but with increased risk of thromboembolic embolic events.	Retrospective systematic review–prior to LMWH use
Meschengieser, 1999 (207) 10377303	Single center experience anticoagulation mechanical valves	92 pregnancies in 59 women	Consecutive unselected pregnancies between 1986–1997	Observational	1. Warfarin throughout pregnancy 2. UFH 1st trimester, then warfarin 3. UFH throughout pregnancy 4. No A/C	Thromboembolic 1. 0.3 episodes/100 pt mo 2. 4.9 episodes/100 pt mo	Fetal wastage 1. 25% 2. 19%	Reduction of thromboembolic events for mother greatest with warfarin throughout pregnancy. No maternal deaths or valve thrombosis occurred in this study.	Retrospective review of small number pts–prior to LMWH use
Vitale, 1999 (208) 10334435	Single center experience anticoagulation mechanical valves	58 pregnancies in 43 pts	Consecutive unselected pregnancies between 1987–1997	Observational	Warfarin throughout pregnancy: A. Dose ≤5 mg vs. B. Dose >5 mg	Maternal Death None Valve thrombosis 2 pts	Fetal complications A. 4 SA and 1 GR (28/32 healthy babies) vs. B: 2 WE, 18 SA, 1 SB, 1 VSD (3/25 healthy babies)	First to show that fetal complications are dose-dependent, relatively safe if dose ≤5 mg	Retrospective review–only warfarin throughout was used
Salazar, 1996 (209) 8636556	Single center experience anticoagulation mechanical valves	40 pregnancies in 37 pts	Single center experience of a prospective protocol using UFH SQ during the 1st trimester	Prospective cohort trial	All pts had SQ UFH from 6–12 wk and then during the last 2 wks of gestation	2 cases of massive thrombosis of a MVR tilting disk. 1 death from GI bleeding during warfarin.	37% spontaneous abortion 2.5% neonatal death No embryopathy	UFH is a poor anticoagulant and does not prevent massive thrombosis	Trial stopped after 2 events occurred
Sbarouni, 1994 (210) 8130033	Questionnaire to all cardiac centers in Europe	214 pregnancies in 182 pts (133 with	Questionnaire sent 1994 to all cardiac centers in Europe	Questionnaire data	N/A	6 maternal deaths (4 valve thrombosis, 1 cerebral embolism, 1 pulmonary edema)	No embryopathies in 36 women on warfarin	Heparin is neither effective or safe for both fetus and mother with increased risk thromboembolism and bleeding	No detailed information on level of anticoagulation

Author, Year	Study Aim	Study Size (N)	Patient Population	Study Type	Type of Anticoagulation	Endpoints		Summary	Study Limitations
						Maternal	***Fetal***		
		mechanical prosthesis)				13 valve thrombosis–10/13 on heparin, 12/13 MVR 8 embolic events–5/8 heparin	Fetal outcome similar for warfarin vs. heparin–22% abortion and 10% stillbirths		dose. Selection bias of those who responded to the questionnaire
Al-Lawati 2002 (211) 12142189	Single center experience anticoagulation mechanical valves from country of Oman	63 pregnancies in 21 pts	Consecutive unselected pregnancies between 1983–1997	Observational	1. Warfarin throughout 2. UFH 1st trimester, then Warfarin	Thrombosis of valves 1. None 2. 2 pts	Fetal complications 1. 74% live babies 2. 71% live babies Spontaneous abortion 1. 26% 2. 14% No embryopathy (2 pts with 6 mg, rest with ≤5 mg)	Role of warfarin embryopathy overstated. Warfarin recommended, especially with low dose of warfarin. Valve thrombosis occurred only in pts with UFH during 1st trimester–none with warfarin.	Retrospective review—only warfarin throughout was used
Sadler 2000 (212) 10688509	Historical cohort of women with mechanical, bioprosthetic and homograft valves from New Zealand	147 pregnancies in 79 pts	All women in New Zealand who had valve replacement 1972–1992 and had subsequent pregnancy	Observational	1. Warfarin throughout pregnancy 2. Warfarin for 6 wk then subq UFH 3. Warfarin for 28 wk then subq UFH	Valve thrombosis 1. 0% 2. 20% 3. 0% Embolic events 1. 0% 2. 20% 3. 25% Hemorrhage 1. 3% 2. 30% 3. 25%	Pregnancy loss 1. 70% 2. 22% 3. 33%	Warfarin had high rate of fetal loss High rate of thromboemboli on heparin (29%) Bioprosthesis or homografts were associated with successful pregnancies	Retrospective review of small number pts—prior to LMWH use
De Santo 2005 (213) 15999035	Single center experience of all pts who had mechanical prosthesis and became pregnant	48 pregnancies in 37 pts	All women from a single center who had MVR 1975 to 2002 and had subsequent pregnancy	Observational	1. Warfarin throughout A. Dose ≤5 mg B. Dose >5 mg 2. 2 pts with UFH	2/2 pts with UFH had valve thrombosis No pt with warfarin had adverse cardiac or valve related event	1A. 2/23 (8.6%) adverse fetal event 1B. 17/21 (81%) adverse fetal event	If continue warfarin throughout pregnancy, there are no maternal events Adverse fetal events mainly if dose >5 mg	Retrospective review of small number pts—prior to LMWH use

AC indicates anticoagulation; GI, gastrointestinal; GR, growth retardation; LMWH, low molecular weight heparin; MVR, mitral valve replacement; N/A, not available; pts, patients; SA, spontaneous abortion; SB, still birth; SQ subcutaneous; UFH, unfractionated heparin; VSD, ventricular septal defect; and, WE, warfarin embryopathy.

2014 Valvular Heart Disease Guideline Data Supplements

Data Supplement 26. Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated With Low Molecular Weight Heparin (LMWH) (Section 13.3.2)

Author, Year	Study Aim	Study Size (N)	Type of Anticoagulant	Patient Population	Study Type	Endpoints		Summary	Study Limitations
						Maternal	*Fetal*		
Rowan 2001 (214) 11568791	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	14 pregnancies in 11 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH single center—1997–1999—fixed dose LMWH	Observational	One valve thrombosis 14.3% hemorrhage	9 live births 3 miscarriages 2 terminations	Can achieve successful pregnancy using LMWH throughout pregnancy, but risk of valve thrombosis	Use fixed dose LMWH with mean anti-Xa level 0.46 pre- and 0.89 post dose. Retrospective review of small number pts.
James, 2006 (215) 16966122	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	76 pregnancies	LMWH throughout pregnancy	Medline search of 73 cases 1966–2006 and 3 of single center using LMWH throughout pregnancy	Meta-analysis	22% thrombotic events 4% maternal mortality	No congenital anomalies 8 spontaneous abortions	Use of LMWH during pregnancy associated with high risk of life threatening thrombosis	No anti X-a levels performed. Meta-analysis only
Abildgaard, 2009 (216) 19162303	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	12 pregnancies in 12 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH throughout pregnancy in country Norway—1997–2008—use anti-Xa levels	Observational	1 systemic embolism and 1 valve thrombosis (both subtherapeutic doses) Pooled risk of thromboembolism 7.1% vs. prior data 25% with UFH	13 healthy babies	If use anti-Xa levels, successful in 10/12 pregnancies, risk lower than UFH by retrospective comparison	Retrospective review of small number pts
Oran, 2004 (217) 15467905	Meta-analysis of pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens, including LMWH	10 reports (2 prospective) 81 pregnancies in 75 women	LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy	Medline search of studies in pts with prostheses receiving LMWH from 1989–2004	Meta-analysis	12% had thromboemboli–all MVR–all with LMWH throughout–9/10 did not have anti-Xa monitoring. Valve thrombosis 8.6%	Spontaneous abortion in 7.4% Stillbirth in 1.2% 87% live births	All thromboemboli occurred in pts with mitral prosthesis who had LMWH throughout pregnancy. Anti Xa levels were not monitored in 90% of thromboembolic events.	Meta-analysis only
McLintock, 2009 (218) 19681850	Examine pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens including LMWH	47 pregnancies in 31 women	Warfarin throughout pregnancy vs. LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy	All pts with mechanical prosthesis treated with differing anticoagulation regimens including LMWH—2 centers—1997–2008—use anti-Xa levels	Observational	Thromboembolism 7 total–5 (10.6%) LMWH Antepartum bleeding 10.6% LMWH Postpartum bleeding 12.7% LMWH	96% live births with LMWH vs. 75% live births with warfarin	Poor compliance or subtherapeutic anti-Xa levels were present in all valve thrombosis on LMWH	Retrospective review of small number pts

Author, Year	Study Aim	Study Size (N)	Type of Anticoagulant	Patient Population	Study Type	Endpoints		Summary	Study Limitations
						Maternal	*Fetal*		
Yinon, 2009 (219) 19840573	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	23 pregnancies in 17 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH—single center 1998–2008—use anti-Xa levels	Observational	1 (4%) maternal thrombosis died 5 (22%) pulmonary edema, arrhythmias, and endocarditis 13% postpartum hemorrhage	19 live births 2 first trimester miscarriages 2 intrauterine deaths	Even with careful monitoring of anti X-a levels thrombosis may occur, even with low risk AVR	Retrospective review of small number pts
Quinn, 2009 (220) 19880782	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	12 pregnancies in 11 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH—single center—2001–2007—use anti-Xa levels	Observational	3 major bleeds 3 minor bleeds BS MVR thrombosis 1 pt (Xa level not done and later subtherapeutic)	11/12 live births	Increasing dose LMWH during pregnancy necessary Only valve thrombosis occurred in pt with subtherapeutic level Xa	Retrospective review of small number pts

AVR indicates aortic valve replacement; BS, Bjork-Shiley; GI, gastrointestinal; LMWH, low molecular weight heparin; MVR, mitral valve replacement; N/A, not available; pts, patients; UFH, unfractionated heparin; and, SES, socioeconomic status.

Data Supplement 27. Outcomes With the Maze Procedure for Atrial Fibrillation in Patients With Valvular Heart Disease (Section 14.2.2)

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
Prognostic Significant of AF at Time of Surgery						
Eguchi et al 2005 (221) 15845559	Examine impact of preoperative AF on outcome of MV repair for 1° MR	Retrospective observational	283 pts with moderate-to-severe MR who underwent MV repair between 1991 and 2002	129 in AF Age 59±13 y 60% male	154 in NSR Age 52±14 y 67% male	5 y outcomes were better in pts in NSR vs. AF for: survival (96±2.1 vs. 87±3.2%; p=0.002) and freedom from cardiac events (96±2.0 vs. 75±4.4%; p<0.001)
Alexiou 2007 (222) 17280837	Impact of preoperative AF on early and late outcome after MV repair	Retrospective observational	349 pts undergoing MV repair for primary MR	152 (44%) in AF	197 (56%) in NSR	Kaplan-Meier survival at 7 y was 75±6% for AF pts vs. 90±3% (p=0.005) for SR pts.
Ngaage 2006 (223) 17643612	Prognostic significance of preoperative AF at the time of AVR	Retrospective observational, cohort comparison	381 AVR 1993 and 2002 matched for age, gender, and LVEF	Preoperative AF (n=129)	Preoperative NSR (n=252)	Pts with preoperative AF had had worse late survival (RR for death=1.5; p=0.03) with 1-, 5-, and 7-y survival rates of 94%, 87%, and 50%, respectively, for those in AF vs. 98%, 90%, and 61% for pts in SR preoperatively. Pts with AF more frequently developed HF (25% vs. 10%; p=0.005) and stroke (16% vs. 5%; p=0.005). By multivariable analysis, preoperative AF was an independent predictor of late adverse cardiac and cerebrovascular events, but not late death.
Predictors of Return of Sinus Rhythm After Valve Surgery						
Chua 1994 (224) 8302059	Determine frequency of reversion to NSR after MV repair among pts with preoperative AF	Retrospective, observational	323 consecutive pts who underwent surgical MV valvuloplasty for MR from 1980–1991	97 in AF before surgery	216 in NSR before surgery	At late follow-up (mean 2.6 y, range 3 mo–10 y), AF was present in 5% pts with preoperative NSR, 80% pts with preoperative chronic AF, and 0% pts with preoperative recent onset AF (p<0.01)
Obadia 1997 (225) 9270633	Determine predictors for return to NSR after MVR	Retrospective, observational	191 pts undergoing surgery for MVR	Preoperative AF in 96 (50%)	Preoperative NSR in 95 (40%)	The probability of return to stable NSR was 93.7% when NSR was already present before the operation and 80% when AF was intermittent or of less than 1 y duration; probability of postop NSR declined abruptly for preoperative duration of AF >1 y
Jessurun 2000 (226) 10814915	Outcome analysis of arrhythmias after MV surgery	Retrospective, observational	162 consecutive pts undergoing MV surgery between 1990 and 1993	Preoperative chronic AF in 74 (46%) and paroxysmal AF in 29 (18%)	Preoperative NSR in 59 (36%)	NSR present postop in 40 of 57 (70%) pts with preop NSR. AF present postop in 58 of 68 (85%) of pts with preop chronic AF (>1 y). NSR present postop in 10 of 29 (34%) pts with preoperative paroxysmal AF.
Outcomes With Surgical Maze for AF						
Deneke 2002 (227) 11922646	Efficacy of a modified maze procedure in pts with chronic AF undergoing MVR	Prospective randomized	30 consecutive pts undergoing MVR	Modified maze at time of MVR	MVR alone	After 12 mo, NSR was present significantly more often in pts undergoing modified maze (cumulative rate NSR=0.800) compared to pts with MV replacement alone (0.267) (p<0.01)

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
Akpinar 2003 (228) 12895612	Assess the feasibility and effectiveness of irrigated RF modified maze procedure through a port access approach during MV surgery	Prospective randomized	67 pts with chronic AF eligible for port access MV surgery	33 irrigated RF modified Maze procedure	34 valve procedure alone	100% of pts who underwent RF modified maze were free of AF at the end of the operation (76% NSR, 24% pacemaker) compared with 41% of those who underwent MV repair alone. At 6 and 12 mo freedom from AF was 87.2 and 93.6% for those undergoing RF maze and 9.4% (p=0.0001) for those undergoing MVR alone
Jessarun 2003 (229) 12627066	Assess outcome of combining the Maze III procedure with MV surgery	Prospective. randomized (2.5:1 ratio)	35 pts with AF undergoing MVR. Mean age 64 y	Maze III in 25	MVR along in 10	Freedom from AF in the maze + MVR group was 56% at discharge and 92% at 12 mo. MVR alone group, freedom from AF was 0% at discharge and 20 at 1 y. Group differences at discharge p=0.002 and at 1 y p=0.0007.
Abreu Filho 2005 (230) 16159816	Evaluate effectiveness of maze procedure for permanent AF in pts with rheumatic MV disease	Prospective randomized	70 consecutive pts (2002−03) with rheumatic MV disease and permanent AF	MV surgery plus Maze III procedure saline-Irrigated cooled-tip RF ablation	MV surgery alone	Cumulative rates of NSR were 79.4% for those undergoing maze and 26.9% for those undergoing mitral surgery alone (p=0.001). Group differences were significant at discharge (p=0.002), after 12 mo (p=0.0007).
Doukas 2005 (231) 16278360	To determine whether intraoperative RF ablation increases the long-term restoration of NSR and improves exercise capacity	Randomized, double-blind trial	97 pts referred for MV surgery with AF for at least 6 mo	MV surgery plus RF left atrial ablation	MV surgery alone	At 12 mo NSR was present in 20 (44.4%) of 45 RFA pts and in 2 (4.5%) of 44 controls, RR: 9.8; 95% CI: 2.4–86.3; p<0.001
Von Oppell 2009 (232) 19233678	Evaluate the effect of maze procedure on postop AF in pts undergoing MV surgery	Prospective randomized	49 pts undergoing MV surgery with AF of more than 6 mo duration in 2004−06	MV surgery plus RF maze procedure (n=24)	MV surgery plus intensive rhythm control strategy (n=25).	At discharge, 3 and 12 mo follow-up, more pts in the maze group returned to NSR compared to control (29%, 57% and 75% vs. 20%, 43% and 39%; p=0.030).
Cheng 2010 (233) 22437354	To determine if surgical maze ablation for AF improves clinical outcomes and resource utilization	Meta-analysis	4647	Adults with persistent and permanent AF undergoing maze surgical ablation at the time of cardiac surgery	Persistent or permanent AF undergoing cardiac surgery without maze procedure	The number of pts in NSR was significantly improved at discharge in the surgical AF ablation group (68.6%) versus the surgery alone group (23.0%) in RCTs (OR: 10.1, 95% CI: 4.5-22.5) and non-RCTs (OR: 7.15, 95% CI: 3.42-14.95). Meta-analysis includes both coronary bypass and valve surgery (numbers not stated).
Long-Term Outcomes After Surgical Maze Procedure						
Bando 2003 (234) 12928631	Identify risk factors for mortality and stroke after mechanical MVR	Retrospective	812 pts undergoing MVR between 1977−2001. Chronic AF present in 630 (78%)	In addition to MVR: 493 (61%) had LV appendage closure 148 (18%) had LA plication 185 (23%) had maze procedure 348 (43%) had tricuspid	Endpoints were early and late mortality and freedom from stroke	At 8 y, freedom from stroke was significantly greater in pts with MVR plus maze (99%) compared to MVR alone (89%, p<0.001) Of 72 pts with late stroke, 65 (90%) were in AF and 47 (65%) had LA appendage closure. Multivariate analysis show that late AF (OR: 3.39; 95% CI: 1.72–6.67; p=.0001) and omission of the maze procedure (OR: 3.40; 95% CI: 1.14–10.14; p=0.003) were significant risk factors for

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
				annuloplasty.		late stroke.
Bum Kim 2012 (235) 22456472	Evaluate long-term benefits of the maze procedure in pts with chronic AF undergoing mechanical MVR	Retrospective, observational	569 pts undergoing mechanical MVR between 1997−2010	317 with MVR plus a concomitant maze procedure	252 with MVR alone	Pts who had undergone the maze procedure were at similar risks of death (HR: 1.15; 95% CI: 0.65–2.03; p=0.63) and the composite outcomes (HR: 0.82; 95% CI: 0.50–1.34; p=0.42), but a significantly lower risk of thromboembolic events (HR: 0.29; 95% CI: 0.12–0.73; p=0.008) compared with those who underwent valve replacement alone
Malaisrie 2012 (236) 22808837	Determine the impact of concomitant AF ablation in pts undergoing AVR	Retrospective, observational	124 pts (mean age 74±12 y) with pre-existing AF undergoing AVR	80 (65%) had concomitant surgical AF ablation	44 had AVR alone	Postop freedom from AF when not receiving anti-arrhythmic drugs occurred in 58 pts (82%) in the ablation group, compared to 8 (36%) in the nonablation group (p<0.001)
Liu 2010 (237) 20573636	Compare pulmonary vein isolation versus maze procedure for treatment of permanent AF	Prospective randomized	99 with rheumatic heart disease and permanent AF	49 with valve surgery plus circumferential pulmonary vein isolation	50 with valve surgery plus maze procedure for AF	After one procedure, pts undergoing the maze procedure had a significantly higher freedom from atrial arrhythmias (82% vs. 55.2%, p<0.001). At 15–20 mo follow-up, cumulative rates of sinus rhythm were 71% vs. 88% (p<0.001).

1° indicates primary; AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; LA, left atrial; LV, left ventricle; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NSR, normal sinus rhythm; preop, preoperative; postop, postoperative; pts, patients; RCT, randomized clinical trial; RF, radiofrequency; RFA, radiofrequency ablation; and, SR, sinus rhythm.

Data Supplement 28. Noncardiac Surgery in Patients With Valvular Heart Disease (Section 15.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints		Predictors of Adverse Outcomes	Study Limitations
					Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*		
Aortic Stenosis										
Agarwal 2013 (238) 23481524	Compared outcomes with noncardiac surgery in pts with moderate vs. severe AS.	Retrospective surgical and echocardiographic database	634 pts with AS; 244 with severe AS and 390 with moderate AS	2,536 controls without AS propensity matched for 6 revised cardiac risk index criteria plus age and sex.	Severe AS defined as valve area <1 cm^2. Moderate AS as valve area 1.0–1.5 cm^2	Emergency surgery.	Combined primary endpoint of 30-d mortality plus MI occurred in 4.9% of pts with AS vs. 2.1% in controls (p<0.001)	30-d mortality was 2.1% for pts with AS vs. 1.0% in non-AS controls (p=0.036). Post-op MI occurred in 3.0% of AS vs 1.1% of controls (p=0.001).	Predictors of adverse outcomes in AS were symptomatic severe AS, MR, coronary disease.	Some pts with AS were symptomatic. Not an RCT.
Calleja 2010 (239) 20381670	Evaluate post-op outcomes of pts with asymptomatic, severe AS	Retrospective	30 pts with asymptomatic severe AS undergoing noncardiac surgery.	60 pts with mild-moderate AS age and sex matched.	Noncardiac surgery, intermediate risk severe AS vs. mild or moderate AS=77% vs. 83%, ASA 3=63% vs. 62%, general anesthesia=73% vs. 82%.	AR >moderate, symptomatic AS.	Composite endpoint (hospital mortality, MI, HF, arrhythmia, and hypotensive requiring vasopressors) in severe AS: 10/30 (33%) vs. 14/60 (23%) in those with mild to moderate AS; p=0.06; MI: 3% in both groups; p=0.74	Hypotension AS severe: 9/30 (30%) vs. AS mild/moderate: 10/60 (17%); p=0.11.	For severe AS: Hypotension OR: 2.5, CI: 0.8–7.6; p=0.11, MI OR: 0.63, CI: 0.04–10; p=0.74.	Use of composite endpoint. Majority of pts underwent intermediate (not high) risk noncardiac surgery.
Leibowitz 2009 (240) 19287130	Outcome of pts with AS undergoing hip fracture repair	Retrospective	Pts with AS (n=32)	Age-matched control (n=88)	Elderly pts >70 y, with AVA <1 cm^2	N/A	30-d mortality AS=6.2%, control=6.8%	Cardiac event rate (death, ACS, pulmonary edema): AS=18.7%, control=11.8%	N/A	Retrospective, 50% of anesthetics were regional techniques
Zahid 2005 (241) 16054477	Evaluate the perioperative risk of noncardiac surgery in pts with AS	Retrospective Based on National Hospital Discharge Survey	AS=5,149	AS-no=10,284 age/surgical risk matched	Noncardiac surgery (1996–2002)	Cardiac surgery	The presence of AS is not a significant predictor for mortality after adjusting for all significant univariate predictor of in-hospital death.	The presence of AS increased the likelihood of AMI (3.86% in AS vs. 2.03% in controls, p<0.001): OR: 1.55, 95% CI: 1.27–1.9; p<0.001	N/A	Pts with AS more likely to have concomitant CAD and CHF, controls more likely to have DM and HTN.
Torsher 1998	Outcomes of pts with AS	Retrospective	Severe AS=19	N/A	Noncardiac	N/A	In selected pts with severe AS, the risk of noncardiac	N/A	N/A	Coexisting mild AR=9, moderate

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints		Predictors of Adverse Outcomes	Study Limitations
					Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*		
(242) 9485135	undergoing noncardiac surgery						surgery is acceptable: Death=2, hypotension was frequent (14 pts)			AR=4, mild MR=12, balloon aortic valvuloplasty=2
Mitral Regurgitation										
Lai 2007 (243) 17383316	Perioperative outcome of pts with MR undergoing noncardiac surgery	Retrospective	84 pts with moderate-severe MR	NA	Undergoing noncardiac surgery	Tracheal intubation prior to noncardiac surgery	Intraoperative course had frequent (31%) minor complications: controllably hypotension and bradycardia	Post-op complications were serious: Death=11.9%, MI=0, Vtach/fib=4.8%, pulmonary edema=23.8%	For post-op complications: AF OR: 3.058, CI: 1.02–9.14, intermediate surgical risk=5.12, CI: 1.28–20.4, low LVEF: 0.96, CI: 0.92–0.99	N/A
Aortic Regurgitation										
Lai 2010 (244) 19930243	Perioperative outcome of chronic, moderate-severe AR who undergo noncardiac surgery	Retrospective (1999–2006)	Chronic, moderate-severe AR=167	Case-matched=167	Chronic moderate-severe AR	N/A	Prolonged intubation and acute pulmonary edema: 16.2% vs. 5.4%; p=0.003, Death: AR=9% vs. 1.8%; p=0.008	LVEF, renal dysfunction, high surgical risk and no cardiac meds predictors of in-hospital death in pts with AR intraoperative hypotension and bradycardia were similar between groups	N/A	N/A

ACS indicates acute coronary syndrome; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, aspirin; AVA, aortic valve area; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; N/A, not applicable; pts, patients; and, post-op, postoperative.

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Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Catherine M. Otto, *(Co-Chair)*	University of Washington Division of Cardiology—Professor of Medicine	None	None	None	None	None	None
Robert O. Bonow	Northwestern University Medical School—Goldberg Distinguished Professor	None	None	None	None	• Gilead • Harvard Clinical Research Institute DAPT trial • NHLBI–PROMISE trial (DSMB) • Society for Heart Valve Disease†	None
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John P. Erwin III	Scott and White Hospital and Clinic—Senior Staff Cardiologist, Associate Professor of Medicine	None	• AHA	None	None	• BRIDGE trial • IMPROVE-IT–PI* • PROMISE–PI • TRANSLATE-ACS–PI*	None
Robert A. Guyton	Emory Clinic, Inc.—Professor and Chief, Division of Cardiothoracic Surgery	• Medtronic	None	None	• NIH†	None	• Defendant, cardiac surgery, 2011 • Defendant, cardiac surgery, 2013
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James D. Thomas	Cleveland Clinic—Professor of Medicine and Biomedical Engineering	None	None	None	None	• American Society of Echocardiography†	None

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*Significant relationship.
†No financial benefit.

AATS indicates American Associate Thoracic Surgery; AHA, American Heart Association; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; DAPT, dual antiplatelet therapy; DSMB, data safety monitoring board; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institute of Health, PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; TRANSLATE-ACS, Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome and VA, Veterans Affairs.

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