Nishimura, RA et al.
2014 AHA/ACC Valvular Heart Disease Guideline

2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary

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

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


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Table of Contents

1. Introduction
   1.1. Methodology and Evidence Review
   1.2. Organization of the Writing Committee
   1.3. Document Review and Approval
   1.4. Scope of the Guideline

2. General Principles
   2.1. Evaluation of the Patient With Suspected VHD
   2.2. Definitions of Severity of Valve Disease
   2.3. Diagnostic Testing—Diagnosis and Follow-Up: Recommendations
   2.4. Basic Principles of Medical Therapy: Recommendations
   2.5. Evaluation of Surgical and Interventional Risk
   2.6. The Heart Valve Team and Heart Valve Centers of Excellence: Recommendations

3. Aortic Stenosis: Recommendations
   3.1. Stages of Valvular AS
   3.2. Diagnosis and Follow-Up
   3.3. Medical Therapy
   3.4. Timing of Intervention
   3.5. Choice of Intervention

4. Aortic Regurgitation: Recommendations
   4.1. Stages of Chronic Aortic Regurgitation
   4.2. Diagnosis and Follow-Up
   4.3. Medical Therapy
   4.4. Timing of Intervention

5. Bicuspid Aortic Valve and Aortopathy: Recommendations
   5.1. Diagnosis and Follow-Up
   5.2. Intervention

6. Mitral Stenosis: Recommendations
   6.1. Stages of MS
   6.2. Diagnosis and Follow-Up
   6.3. Medical Therapy
   6.4. Intervention

7. Mitral Regurgitation: Recommendations
   7.1. Stages of Chronic MR
   7.2. Chronic Primary MR
   7.2.1. Diagnosis and Follow-Up
   7.2.2. Medical Therapy
   7.2.3. Intervention
   7.3. Chronic Secondary MR
   7.3.1. Diagnosis and Follow-Up
   7.3.2. Medical Therapy
   7.3.3. Intervention

8. Tricuspid Valve Disease: Recommendations
   8.1. Stages of TR
   8.2. Tricuspid Regurgitation
   8.2.1. Diagnosis and Follow-Up
   8.2.2. Medical Therapy
   8.2.3. Intervention
   8.3. Stages of Tricuspid Stenosis
   8.4. Tricuspid Stenosis
   8.4.1. Diagnosis and Follow-Up
   8.4.2. Intervention

9. Stages of Pulmonic Valve Disease

10. Prosthetic Valves: Recommendations
    10.1. Evaluation and Selection of Prosthetic Valves
    10.1.1. Diagnosis and Follow-Up

Page 3 of 96
Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant) .............................................................. 69

References .............................................................................................................................................................................. 80

12. Pregnancy and VHD: Recommendations ......................................................................................................................... 57

12.1. Native Valve Stenosis ............................................................................................................................................... 57
  12.1.1. Diagnosis and Follow-Up .................................................................................................................................. 58
  12.1.2. Medical Therapy .................................................................................................................................................. 58
  12.1.3. Intervention ....................................................................................................................................................... 58

12.2. Native Valve Regurgitation ...................................................................................................................................... 59
  12.2.1. Diagnosis and Follow-Up .................................................................................................................................. 59
  12.2.2. Medical Therapy .................................................................................................................................................. 59
  12.2.3. Intervention ....................................................................................................................................................... 59

12.3. Prosthetic Valves in Pregnancy ................................................................................................................................ 60
  12.3.1. Diagnosis and Follow-Up .................................................................................................................................. 60
  12.3.2. Medical Therapy .................................................................................................................................................. 60

13. Surgical Considerations: Recommendations .................................................................................................................. 63

13.1. Evaluation of Coronary Anatomy ............................................................................................................................... 63

13.2. Concomitant Procedures ........................................................................................................................................... 63
  13.2.1. Intervention for CAD ......................................................................................................................................... 63
  13.2.2. Intervention for AF ............................................................................................................................................. 64

14. Noncardiac Surgery in Patients With VHD: Recommendations ....................................................................................... 65

Appendix 1. Author Relationships With Industry and Other Entities (Relevant) ................................................................. 66
Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant) ................................................................. 69
References .............................................................................................................................................................................. 80
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.

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.
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
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.0000000000000029/-/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. The reader is encouraged to consult the full-text guideline (4) for additional guidance and details about valvular heart disease (VHD), since the executive summary contains only the recommendations.
Table 1. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple populations evaluated^</td>
<td>Limited populations evaluated^</td>
<td>Very limited populations evaluated^</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

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 were reviewed by the guideline writing committee. The relevant data are included in evidence tables in the Data Supplement available online at (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000029/-/DC1). 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 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 the 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 (5). 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.

The full-text version of this guideline (4) 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 relevant data are included in evidence tables in the Data Supplement of the full-text guideline (4).

The present document applies to adult patients with VHD. Management of patients with congenital heart disease (CHD) 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

<table>
<thead>
<tr>
<th>Title</th>
<th>Organization</th>
<th>Publication Year/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations for Evaluation of the Severity of Native Valvular</td>
<td>ASE</td>
<td>2003 (6)</td>
</tr>
<tr>
<td>Regurgitation With Two-Dimensional and Doppler Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidelines for the Management of Patients With Atrial Fibrillation</td>
<td>ACC/AHA/ESC</td>
<td>2006 (7)*</td>
</tr>
<tr>
<td>Guidelines for the Management of Adults With Congenital Heart</td>
<td>ACC/AHA</td>
<td>2008 (8)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiographic Assessment of Valve Stenosis: EAE/ASE</td>
<td>EAE/ASE</td>
<td>2009 (9)</td>
</tr>
<tr>
<td>Recommendations for Clinical Practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound</td>
<td>ASE</td>
<td>2009 (10)</td>
</tr>
<tr>
<td>Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy</td>
<td>ACCF/AHA</td>
<td>2011 (11)</td>
</tr>
<tr>
<td>Guidelines on the Management of Cardiovascular Diseases During</td>
<td>ESC</td>
<td>2011 (12)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic and Thrombolytic Therapy for Valvular</td>
<td>ACCP</td>
<td>2012 (13)</td>
</tr>
</tbody>
</table>
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, as well as a chest x-ray and electrocardiogram. A comprehensive transthoracic echocardiogram (TTE) with 2-dimensional 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” (18). 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 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 3.1 (Table 6), Section 4.1 (Table 9), Section 6.1 (Table 11), Section 7.1 (Tables 13 and 14), Section 8.1 (Table 17), Section 8.3 (Table 18), and Section 9 (Tables 19 and 20).

Table 3. Stages of Progression of VHD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk</td>
<td>Patients with risk factors for development of VHD</td>
</tr>
<tr>
<td>B</td>
<td>Progressive</td>
<td>Patients with progressive VHD (mild-to-moderate severity and asymptomatic)</td>
</tr>
</tbody>
</table>
| 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.

2.3. Diagnostic Testing—Diagnosis and Follow-Up: Recommendations

See Table 4 for the frequency of echocardiograms in asymptomatic patients with VHD and normal left ventricular function.

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 (19-34). *(Level of Evidence: B)*

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

3. 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)*

4. 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)*

**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 (35-39). *(Level of Evidence: B)*

**Table 4. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal Left Ventricular Function**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Valve Lesion</th>
<th>Aortic Stenosis*</th>
<th>Aortic Regurgitation</th>
<th>Mitral Stenosis</th>
<th>Mitral Regurgitation</th>
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</thead>
<tbody>
<tr>
<td>Progressive</td>
<td></td>
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<tr>
<td>(stage B)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Every 3–5 y</td>
<td>Every 3–5 y</td>
<td>Every 3–5 y</td>
<td>Every 3–5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mild severity)</td>
<td>(mild severity)</td>
<td>(MVA &gt;1.5 cm²)</td>
<td>(mild severity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0–2.9 m/s</td>
<td>1–2 y (moderate</td>
<td>Every 1–2 y</td>
<td>Every 1–2 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>severity)</td>
<td>(MVA 1.0–1.5 cm²)</td>
<td>(moderate severity)</td>
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<tr>
<td></td>
<td></td>
<td>every 1–2 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(moderate severity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>V_max 3.0–3.9 m/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>Every 6–12 mo</td>
<td>Every 6–12 mo</td>
<td>Every 1–2 y</td>
<td>Every 6–12 mo</td>
</tr>
<tr>
<td>(stage C)</td>
<td></td>
<td>(V_max ≥4 m/s)</td>
<td>Dilating LV: more</td>
<td>(MVA &lt;1.0 cm²)</td>
<td>Dilating LV: more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>frequently</td>
<td></td>
<td>frequently</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

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.

**2.4. Basic Principles of Medical Therapy: Recommendations**

**Class I**

1. Secondary prevention of rheumatic fever is indicated in patients with rheumatic heart disease, specifically mitral stenosis (MS) (40). *(Level of Evidence: C)*

**Class IIa**

1. Prophylaxis against infective endocarditis (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 (41-43), *(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 CHD with:
     - Unrepaired cyanotic CHD, including palliative shunts and conduits;
     - 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 CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.

**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 (44). *(Level of Evidence: B)*

2.5. Evaluation of Surgical and Interventional Risk

See Table 5 for risk assessment combining STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments.

Table 5. Risk Assessment Combining STS Risk Estimate, Frailty, Major Organ System Dysfunction, and Procedure-Specific Impediments

<table>
<thead>
<tr>
<th>Low Risk (Must Meet ALL Criteria in This Column)</th>
<th>Intermediate Risk (Any 1 Criterion in This Column)</th>
<th>High Risk (Any 1 Criterion in This Column)</th>
<th>Prohibitive Risk (Any 1 Criterion in This Column)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS PROM* &lt;4% AND 4% to 8% OR &gt;8% OR Predicted risk with surgery of death or major morbidity (all-cause) &gt;50% at 1 y OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty† None AND 1 Index (mild) OR ≥2 Indices (moderate to severe) OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure-specific impediment§ None Possible procedure-specific impediment Possible procedure-specific impediment Severe procedure-specific impediment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 DLCO2 <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; DLCO2, 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

Class I

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

Class IIa
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)

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 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 aortic stenosis (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.
3. Aortic Stenosis: Recommendations

See Table 6 for the stages of valvular AS; Tables 7 and 8 for a summary of recommendations for choice and timing of intervention; and Figure 1 for indications for AVR in patients with AS.

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 6 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 left ventricular (LV) systolic dysfunction with a low left ventricular 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 >4.0 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 cm². At normal flow rates, an aortic valve area of <0.8 cm² correlates with a mean aortic valve gradient >40 mm Hg. However, symptomatic patients with a calcified aortic valve with reduced opening and an aortic valve area between 0.8 cm² and 1.0 cm² 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.
## Table 6. Stages of Valvular AS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| 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 $\Delta P <$20 mm Hg  
• Moderate AS:  
Aortic $V_{max}$ 3.0–3.9 m/s or mean $\Delta P$ 20–39 mm Hg | Early LV diastolic dysfunction may be present  
Normal LVEF | None |
| C     | Asymptomatic severe AS | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically is $\leq 1.0$ cm$^2$ (or $\text{AVAi} \leq 0.6$ cm$^2$/m$^2$)  
• Very severe AS is an aortic $V_{max} \geq 5$ m/s or mean $\Delta P$ 60 mm Hg | LV diastolic dysfunction  
Mild LV hypertrophy  
Normal LVEF | None: Exercise testing is reasonable to confirm symptom status |
| C1    | Asymptomatic severe AS | | | | |
| C2    | Asymptomatic severe AS with LV dysfunction | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically $\leq 1.0$ cm$^2$ (or AVAi $\leq 0.6$ cm$^2$/m$^2$) | LVEF <50% | None |
| D     | Symptomatic severe AS | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically $\leq 1.0$ cm$^2$ (or AVAi $\leq 0.6$ 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 | |
| D1    | Symptomatic severe high-gradient AS | | | | |
| D2    | Symptomatic severe low-flow/low-gradient AS with reduced LVEF | • Severe leaflet calcification with severely reduced leaflet motion | • AVA $\leq 1.0$ cm$^2$ with resting aortic $V_{max} < 4$ m/s or mean $\Delta P <$40 mm Hg  
• Dobutamine stress echocardiography shows AVA $\leq 1.0$ cm$^2$ with $V_{max} \geq 4$ m/s at any flow rate | LV diastolic dysfunction  
LV hypertrophy  
LVEF <50% | HF  
Angina  
Syncope or presyncope |
| D3    | Symptomatic severe low-gradient AS | | | | HF  
Increased LV |
### AS with normal LVEF or paradoxical low-flow severe AS

<table>
<thead>
<tr>
<th>with severely reduced leaflet motion</th>
<th>mean ΔP &lt;40 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Indexed AVA ≤0.6 cm²/m² and</td>
</tr>
<tr>
<td></td>
<td>• Stroke volume index &lt;35 mL/m²</td>
</tr>
<tr>
<td></td>
<td>• Measured when patient is normotensive (systolic BP &lt;140 mm Hg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>relative wall thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small LV chamber with low stroke volume</td>
</tr>
<tr>
<td>• Restrictive diastolic filling</td>
</tr>
<tr>
<td>• LVEF ≥50%</td>
</tr>
</tbody>
</table>

- 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 $V_{\text{max}}$, maximum aortic velocity.
### 3.2. 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.

**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 (26, 27, 45). *(Level of Evidence: B)*

**Class IIa**

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 (46-48), *(Level of Evidence: B)*:
   a. Calcified aortic valve with reduced systolic opening;
   b. LVEF less than 50%;
   c. Calculated valve area 1.0 cm² or less; and
   d. Aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg.

2. 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) (27, 37, 38, 49). *(Level of Evidence: B)*

**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) (50). *(Level of Evidence: B)*

### 3.3. Medical Therapy

**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 (51-53). *(Level of Evidence: B)*

**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 New York Heart Association (NYHA) class IV heart failure (HF) symptoms. *(Level of Evidence: C)*

**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) (54-56). *(Level of Evidence: A)*

### 3.4. Timing of Intervention

See Table 7 for a summary of recommendations from this section.
1. AVR is recommended in symptomatic patients with severe AS (stage D1) with (57-60), (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.

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 (61, 62). (Level of Evidence: B)

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 (63, 64). (Level of Evidence: B)

Class IIa

1. AVR is reasonable for asymptomatic patients with very severe AS (stage C1) with (65, 66), (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.

2. AVR is reasonable in apparently asymptomatic patients with severe AS (stage C1) with (27, 38), (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 blood pressure (BP).

3. AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a (67-69), (Level of Evidence: B):
   a. Calcified aortic valve with reduced systolic opening;
   b. Resting valve area 1.0 cm² or less;
   c. Aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg;
   d. LVEF less than 50%; and
   e. A low-dose dobutamine stress study that shows an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher with a valve area 1.0 cm² or less at any dobutamine dose.

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 cm² 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 4.0 m per second or mean pressure gradient less than 40 mm Hg; and
   b. A stroke volume index less than 35 mL/m²; and
   c. An indexed valve area 0.6 cm²/m² or less.

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)
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/s or greater per year. *(Level of Evidence: C)*

### Table 7. Summary of Recommendations for AS: Timing of Intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR is recommended with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1)</td>
<td>I</td>
<td>B</td>
<td>(10, 57-59)</td>
</tr>
<tr>
<td>AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF &lt;50%</td>
<td>I</td>
<td>B</td>
<td>(61, 62)</td>
</tr>
<tr>
<td>AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery</td>
<td>I</td>
<td>B</td>
<td>(63, 64)</td>
</tr>
<tr>
<td>AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥5.0 m/s) and low surgical risk</td>
<td>IIa</td>
<td>B</td>
<td>(65, 66)</td>
</tr>
<tr>
<td>AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP</td>
<td>IIa</td>
<td>B</td>
<td>(27, 38)</td>
</tr>
<tr>
<td>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 cm² at any dobutamine dose</td>
<td>IIa</td>
<td>B</td>
<td>(67-69)</td>
</tr>
<tr>
<td>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</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AVR is reasonable for patients with moderate AS (stage B) (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.

**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/m², indexed AVA is ≤0.6 cm²/m², 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; ΔPmean, mean pressure gradient; and Vmax, maximum velocity.

### 3.5. Choice of Intervention

See Table 8 for a summary of recommendations from this section.

#### Class I

1. Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.4) with low or intermediate surgical risk (Section 2.5 in the full-text guideline) (70, 71). *(Level of Evidence: A)*

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)*
3. TAVR is recommended in patients who meet an indication for AVR (Section 3.4) who have a prohibitive risk for surgical AVR (Section 2.5 in the full-text guideline) and a predicted post-TAVR survival greater than 12 months (72, 73). (Level of Evidence: B)

Class IIa
1. TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.4) and who have high surgical risk for surgical AVR (Section 2.5 in the full-text guideline) (74, 75). (Level of Evidence: B)

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)

Class III: No Benefit
1. TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (72). (Level of Evidence: B)

Table 8. Summary of Recommendations for AS: Choice of Surgical or Transcatheter Intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.4) with low or intermediate surgical risk (Section 2.5 in the full-text guideline)</td>
<td>I</td>
<td>A</td>
<td>(70, 71)</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>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 &gt;12 mo</td>
<td>I</td>
<td>B</td>
<td>(72, 73)</td>
</tr>
<tr>
<td>TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.4) and who have high surgical risk (Section 2.5 in the full-text guideline)</td>
<td>IIa</td>
<td>B</td>
<td>(74, 75)</td>
</tr>
<tr>
<td>Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS</td>
<td>III: No Benefit</td>
<td>B</td>
<td>(72)</td>
</tr>
</tbody>
</table>

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.

4. Aortic Regurgitation: Recommendations

4.1. Stages of Chronic Aortic Regurgitation
The most common causes of chronic aortic regurgitation (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 9 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 defined by valve anatomy, valve hemodynamics, severity of LV dilation, and LV systolic function, as well as by patient symptoms.
Nishimura, RA et al.
2014 AHA/ACC Valvular Heart Disease Guideline

**Table 9. Stages of Chronic AR**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| 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:  
- Jet width <25% of LVOT;  
- Vena contracta <0.3 cm;  
- RVol <30 mL/beat;  
- RF <30%;  
- ERO <0.10 cm²;  
- Angiography grade 1+  

- Moderate AR:  
- Jet width 25%–64% of LVOT;  
- Vena contracta 0.3–0.6 cm;  
- RVol 30–59 mL/beat;  
- RF 30%–49%;  
- ERO 0.10–0.29 cm²;  
- 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:  
- Jet width ≥65% of LVOT;  
- Vena contracta >0.6 cm;  
- Holodiastolic flow reversal in the proximal abdominal aorta  
- RVol ≥60 mL/beat;  
- RF ≥50%;  
- ERO ≥0.3 cm²;  
- Angiography grade 3+ to 4+;  
- 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/m²) | • None; exercise testing is reasonable to confirm symptom status |
### 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:

- Doppler jet width $\geq 65\%$ of LVOT;
- Vena contracta $> 0.6$ cm,
- Holodiastolic flow reversal in the proximal abdominal aorta,
- $RVol \geq 60$ mL/beat;
- $RF \geq 50\%$;
- $ERO \geq 0.3$ cm$^2$;
- Angiography grade 3+ to 4+;
- In addition, diagnosis of chronic severe AR requires evidence of LV dilation

### Symptomatic severe AR may occur with normal systolic function ($LVEF \geq 50\%$), 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.
Nishimura, RA et al.  
2014 AHA/ACC Valvular Heart Disease Guideline

See Figure 2 for indications for AVR for chronic AR

### 4.2. Diagnosis and Follow-Up

**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** (34, 76-85). *(Level of Evidence: B)*

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** (86). *(Level of Evidence: B)*

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** (87, 88). *(Level of Evidence: B)*

### 4.3. Medical Therapy

**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 angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs)** (84, 89). *(Level of Evidence: B)*

**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** (90, 91). *(Level of Evidence: B)*

### 4.4. Timing of Intervention

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

**Class I**

1. **AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D)** (33, 92, 93). *(Level of Evidence: B)*

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** (92, 94-96). *(Level of Evidence: B)*

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

**Class IIa**

1. **AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%) but with severe LV dilatation (LV end-systolic dimension [LVESD] >50 mm or indexed LVESD >25 mm/m²) (stage C2)** (97-99). *(Level of Evidence: B)*

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

**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)*
**Table 10. Summary of Recommendations for AR Intervention**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D)</td>
<td>I</td>
<td>B</td>
<td>(33, 92, 93)</td>
</tr>
<tr>
<td>AVR is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF &lt;50%) (stage C2)</td>
<td>I</td>
<td>B</td>
<td>(92, 94-96)</td>
</tr>
<tr>
<td>AVR is indicated for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%) but with severe LV dilation (LVESD &gt;50 mm, stage C2)</td>
<td>IIa</td>
<td>B</td>
<td>(97-99)</td>
</tr>
<tr>
<td>AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>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 &gt;65 mm) if surgical risk is low*</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*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.

**Figure 2. Indications for AVR for Chronic AR**

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; and N/A, not applicable.
ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; and RVol, regurgitant volume.

5. Bicuspid Aortic Valve and Aortopathy: Recommendations

5.1. Diagnosis and Follow-Up

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 (100-105). (Level of Evidence: B)

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)

3. 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)

5.2. Intervention

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 (106-108). (Level of Evidence: B)

Class IIa

1. Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with a bicuspid aortic valve 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)

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 3.4 and 4.4) if the diameter of the ascending aorta is greater than 4.5 cm. (Level of Evidence: C)

6. Mitral Stenosis: Recommendations

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 11 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 the full
text) 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 \( \leq 1.5 \text{ cm}^2 \) 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 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 (109-115).
### Table 11. Stages of MS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of MS</td>
<td>• Mild valve doming during diastole</td>
<td>Normal transmitral flow velocity</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Progressive MS</td>
<td>• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA &gt;1.5 cm²</td>
<td>• Increased transmitral flow velocities • MVA &gt;1.5 cm² • Diastolic pressure half-time &lt;150 ms</td>
<td>• Mild-to-moderate LA enlargement • Normal pulmonary pressure at rest</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe MS</td>
<td>• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm² • (MVA ≤1.0 cm² with very severe MS)</td>
<td>• MVA ≤1.5 cm² • (MVA ≤1.0 cm² with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)</td>
<td>• Severe LA enlargement • Elevated PASP &gt;30 mm Hg</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe MS</td>
<td>• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm²</td>
<td>• MVA ≤1.5 cm² • (MVA ≤1.0 cm² with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)</td>
<td>• Severe LA enlargement • Elevated PASP &gt;30 mm Hg</td>
<td>• Decreased exercise tolerance • Exertional dyspnea</td>
</tr>
</tbody>
</table>

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.
6.2. Diagnosis and Follow-Up

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) (9, 60, 116-123). \(^{(Level \ of \ Evidence: \ B)}\)

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 mitral regurgitation (MR) (117, 124-126). \(^{(Level \ of \ Evidence: \ B)}\)

3. 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. \(^{(Level \ of \ Evidence: \ C)}\)

6.3. Medical Therapy

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 (127-133). \(^{(Level \ of \ Evidence: \ B)}\)

Class IIa
1. Heart rate control can be beneficial in patients with MS and AF and fast ventricular response. \(^{(Level \ of \ Evidence: \ C)}\)

Class IIb
1. Heart rate control may be considered for patients with MS in normal sinus rhythm and symptoms associated with exercise (134, 135). \(^{(Level \ of \ Evidence: \ B)}\)

6.4. Intervention

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

Class I
1. Percutaneous mitral balloon commissurotomy is recommended for symptomatic patients with severe MS (mitral valve area \(\leq 1.5 \text{ cm}^2\), stage D) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (109-113, 115, 136). \(^{(Level \ of \ Evidence: \ A)}\)

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 \(\leq 1.5 \text{ cm}^2\), stage D) who are not high risk for surgery and who are not candidates for or who have failed previous percutaneous mitral balloon commissurotomy (137-142). \(^{(Level \ of \ Evidence: \ B)}\)

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

Class IIa
1. Percutaneous mitral balloon commissurotomy is reasonable for asymptomatic patients with very severe MS (mitral valve area \(\leq 1.0 \text{ cm}^2\), stage C) and favorable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR (121, 143-145). \(^{(Level \ of \ Evidence: \ C)}\)
2. Mitral valve surgery is reasonable for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area \(\leq 1.5\) cm\(^2\), stage D), provided there are other operative indications (e.g., aortic valve disease, coronary artery disease (CAD), tricuspid regurgitation (TR), aortic aneurysm). (Level of Evidence: C)

Class IIb

1. Percutaneous mitral balloon commissurotomy may be considered for asymptomatic patients with severe MS (mitral valve area \(\leq 1.5\) 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)

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)

3. Percutaneous mitral balloon commissurotomy may be considered for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area \(\leq 1.5\) 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)

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)

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

Table 12. Summary of Recommendations for MS Intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>I</td>
<td>A</td>
<td>(109-113, 115)</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>B</td>
<td>(137-142)</td>
</tr>
<tr>
<td>Concomitant mitral valve surgery is indicated for patients with severe MS (MVA (\leq 1.1) cm(^2), stage C or D) undergoing other cardiac surgery</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>PMBC is reasonable for asymptomatic patients with very severe MS (MVA (\leq 1.0) cm(^2), stage C) and favorable valve morphology in the absence of contraindications</td>
<td>IIa</td>
<td>C</td>
<td>(121, 143-145)</td>
</tr>
<tr>
<td>Mitral valve surgery is reasonable for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA (\leq 1.5) cm(^2), stage D), provided there are other operative indications</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>PMBC may be considered for asymptomatic patients with severe MS (MVA (\leq 1.5) cm(^2), stage C) and favorable valve morphology who have new onset of AF in the absence of contraindications</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>PMBC may be considered for symptomatic patients with MVA &gt;1.5 cm(^2) if there is evidence of hemodynamically significant MS during exercise</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>PMBC may be considered for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA (\leq 1.5) cm(^2), stage D) who have suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Concomitant mitral valve surgery may be considered for patients with moderate MS (MVA 1.6–2.0 cm(^2)) undergoing other cardiac surgery</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Mitral valve surgery and excision of the left atrial appendage may be</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>
considered for patients with severe MS (MVA ≤ 1.5 cm², stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation.

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.

**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.

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**7. Mitral Regurgitation: Recommendations**

**7.1. 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 13). 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 14). Instead, severe LV dysfunction is caused either by CAD, related myocardial infarction (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 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 due to the associated progressive LV systolic dysfunction and adverse remodeling. In addition, there is an underestimation of effective regurgitant orifice area by the 2-dimensional 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.
### Table 13. Stages of Primary MR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics*</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| 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 cm²  
• 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 cm²  
• 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 cm²  
• 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.
### Table 14. Stages of Secondary MR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics*</th>
<th>Associated Cardiac Findings</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of MR</td>
<td>• Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy</td>
<td>• No MR jet or small central jet area &lt;20% LA on Doppler • Small vena contracta &lt;0.30 cm</td>
<td>• 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</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td>B</td>
<td>Progressive MR</td>
<td>• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets</td>
<td>• ERO &lt;0.20 cm²† • Regurgitant volume &lt;30 mL • Regurgitant fraction &lt;50%</td>
<td>• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe MR</td>
<td>• 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</td>
<td>• ERO ≥0.20 cm²† • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%</td>
<td>• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe MR</td>
<td>• 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</td>
<td>• ERO ≥0.20 cm²† • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%</td>
<td>• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td>HF symptoms due to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea</td>
</tr>
</tbody>
</table>

*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.
7.2. Chronic Primary MR

7.2.1. Diagnosis and Follow-Up

Class I

1. TTE is indicated for baseline evaluation of LV size and function, right ventricular (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 (6, 23, 146-162). (Level of Evidence: B)

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 (157, 163, 164). (Level of Evidence: B)

3. Intraoperative TEE is indicated to establish the anatomic basis for chronic primary MR (stages C and D) and to guide repair (165, 166). (Level of Evidence: B)

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)

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) (167, 168). (Level of Evidence: B)

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)

7.2.2. Medical Therapy

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 (169-173). (Level of Evidence: B)

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 (173-178). (Level of Evidence: B)

7.2.3. Intervention

See Table 15 for a summary of recommendations from this section.

Class I

1. Mitral valve surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF greater than 30% (156, 179). (Level of Evidence: B)

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) (150-153, 180-182). (Level of Evidence: B)

3. Mitral valve repair is recommended in preference to mitral valve replacement (MVR) when surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet (155, 183-198). (Level of Evidence: B)

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 (195-197, 199-203). (Level of Evidence: B)
5. Concomitant mitral valve repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications (204). *(Level of Evidence: B)*

**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 expected mortality rate of less than 1% when performed at a Heart Valve Center of Excellence (149, 203, 205-209). *(Level of Evidence: B)*

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) (154, 205, 210-215). *(Level of Evidence: B)*

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)*

**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)*

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 (194, 202, 203). *(Level of Evidence: B)*

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 (216). *(Level of Evidence: B)*

**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 (195-198). *(Level of Evidence: B)*

---

**Table 15. Summary of Recommendations for Chronic Primary MR**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF &gt;30%</td>
<td>I</td>
<td>B</td>
<td>(156, 179)</td>
</tr>
<tr>
<td>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)</td>
<td>I</td>
<td>B</td>
<td>(150-153, 180-182)</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>B</td>
<td>(155, 183-198)</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>B</td>
<td>(195-197, 199-203)</td>
</tr>
<tr>
<td>Concomitant MV repair or replacement is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications</td>
<td>I</td>
<td>B</td>
<td>(204)</td>
</tr>
</tbody>
</table>
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

MV repair is reasonable for asymptomatic patients with chronic severe 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)

Concomitant MV repair is reasonable in patients with chronic moderate primary MR (stage B) undergoing cardiac surgery for other indications

MV surgery may be considered in symptomatic patients with chronic moderate primary MR and LVEF ≤30% (stage D)

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

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

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

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.

7.3. Chronic Secondary MR

7.3.1. Diagnosis and Follow-Up

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)

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)

7.3.2. Medical Therapy

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 (128, 217-221). (Level of Evidence: A)

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 (222, 223). (Level of Evidence: A)
7.3.3. Intervention

See Table 16 for a summary of recommendations for this section and Figure 4 for indications for surgery for MR.

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)*

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 (224-235). *(Level of Evidence: B)*
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)*

Table 16. Summary of Recommendations for Chronic Severe Secondary MR

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>MV surgery may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe secondary MR (stage D)</td>
<td>IIb</td>
<td>B</td>
<td>(224-235)</td>
</tr>
<tr>
<td>MV repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.

Figure 4. Indications for Surgery for MR.
Mitral Regurgitation

Primary MR

Severe MR
Vena contracta ≥0.7 cm
RVol ≥60 mL
RF ≥50%
ERO ≥0.4 cm²
LV dilation

Symptomatic (stage D)
LVEF >30%

Asymptomatic (stage C)
LVEF 30% to ≤60%
or LVESD ≥40 mm
(stage C2)
LVEF ≤60% and
LVESD < 40 mm
(stage C1)
New onset AF or
PASP >50 mm Hg
(stage C1)

Likelihood of successful repair = 95% and
Expected mortality = 1%

MV Surgery*(IIa)
MV Surgery*(IIa)
MV Repair (IIa)
Periodic Monitoring

Secondary MR

Progressive MR
Vena contracta < 0.7 cm
RVol < 60 mL
RF < 50%
ERO < 0.4 cm²

Symptomatic severe MR (stage D)
Asymptomatic severe MR (stage C)
Progressive MR (stage B)

Persistent NYHA class III-IV symptoms

CAD Rx
HF Rx
Consider CRT

*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: Recommendations

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 17 shows the stages (A through D) of primary and functional TR as defined for other valve 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: (236)
**Nishimura, RA et al.**  
2014 AHA/ACC Valvular Heart Disease Guideline

**Table 17. Stages of TR**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics*</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| 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) | • No or trace TR | • None | • None or in relation to other left heart or pulmonary/pulmonary vascular disease |
|       |            | **Functional**  
   - Normal  
   - Early annular dilation | | | |
| B     | Progressive TR | **Primary**  
   - Progressive leaflet deterioration/destruction  
   - Moderate-to-severe prolapse, limited chordal rupture | **Mild TR**  
   - Central jet area <5.0 cm²  
   - Vena contracta width not defined  
   - CW jet density and contour: soft and parabolic  
   - Hepatic vein flow: systolic dominance | **Mild TR**  
   - RV/RA/IVC size normal | • None or in relation to other left heart or pulmonary/pulmonary vascular disease |
|       |            | **Functional**  
   - Early annular dilation  
   - Moderate leaflet tethering | **Moderate TR**  
   - Central jet area 5–10 cm²  
   - Vena contracta width not defined but <0.70 cm  
   - CW jet density and contour: dense, variable contour  
   - Hepatic vein flow: systolic blunting | **Moderate TR**  
   - No RV enlargement  
   - No or mild RA enlargement  
   - No or mild IVC enlargement with normal respirophasic variation  
   - Normal RA pressure | |
| C     | Asymptomatic, severe TR | **Primary**  
   - Flail or grossly distorted leaflets | • Central jet area >10.0 cm²  
   - Vena contracta width >0.7 cm  
   - CW jet density and contour: dense, triangular with early peak  
   - Hepatic vein flow: systolic | **RH/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 |
|       |            | **Functional**  
   - Severe annular dilation | | | |
### Nishimura, RA et al.  
**2014 AHA/ACC Valvular Heart Disease Guideline**

<table>
<thead>
<tr>
<th></th>
<th>(&gt;40 mm or 21 mm/m²)</th>
<th>reversal</th>
<th>septal flattening may be present</th>
</tr>
</thead>
</table>
| **D** | Symptomatic severe TR | **Primary** | • Central jet area >10.0 cm²  
• 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 |
|     | **Functional** | Marked leaflet tethering |                                    |
|     | • Flail or grossly distorted leaflets  
• Severe annular dilation (>40 mm or >21 mm/m²)  
• Marked leaflet tethering |                                    |                                    |

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

8.2.1. Diagnosis and Follow-Up

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)

Class IIa
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)

Class IIb
1. CMR or real-time 3-dimensional 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 2-dimensional echocardiograms. (Level of Evidence: C)
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)

8.2.2. Medical Therapy

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

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)

8.2.3. Intervention

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)

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 (237-246). (Level of Evidence: B)
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)

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)
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)*

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

Figure 5. Indications for Surgery

---

8.3. Stages of Tricuspid Stenosis

See Table 18 for the stages of severe tricuspid stenosis (TS).

Table 18. Stages of Severe TS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| C, D  | Severe TS  | ● Thickened, distorted, calcified leaflets | ● T ½ ≥190 ms  
 ● Valve area ≤1.0 cm² | ● RA/IVC enlargement | ● None or variable and dependent on severity of associated valve disease and degree of |
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.

Nishimura, RA et al. 2014 AHA/ACC Valvular Heart Disease Guideline

8.4. Tricuspid Stenosis

8.4.1. Diagnosis and Follow-Up

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)

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)

8.4.2. Intervention

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

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

9. Stages of Pulmonic Valve Disease

See Table 19 for the stages of severe pulmonic regurgitation and Table 20 for the stages of severe pulmonic stenosis.

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

CW indicates continuous wave; PR, pulmonic regurgitation; RV, right ventricular; and RVOT, right ventricular outflow tract. (247)
Stage | Definition | Valve Anatomy | Valve Hemodynamics | Hemodynamic Consequences | Symptoms
--- | --- | --- | --- | --- | ---
C, D | Severe PS | Thickened, distorted, possibly calcified leaflets with systolic doming and/or reduced excursion | \( V_{\text{max}} > 4 \text{ m/s}; \) peak instantaneous gradient \( > 64 \text{ mm Hg} \) | RVH | None or variable and dependent on severity of obstruction

Other anatomic abnormalities may be present, such as narrowed RVOT

Vmax, maximal pulmonic valve jet velocity.

**10. Prosthetic Valves: Recommendations**

**10.1. Evaluation and Selection of Prosthetic Valves**

**10.1.1. Diagnosis and Follow-Up**

**Class I**

1. An initial TTE study is recommended in patients after prosthetic valve implantation for evaluation of valve hemodynamics (248-251). *(Level of Evidence: B)*
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)*
3. TEE is recommended when clinical symptoms or signs suggest prosthetic valve dysfunction. *(Level of Evidence: C)*

**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)*

**10.1.2. Intervention**

See Table 21 for a summary of recommendations for prosthetic valve choice.

**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)*
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)*

**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 (252-254). *(Level of Evidence: B)*
2. A bioprosthesis is reasonable in patients more than 70 years of age (255-258). *(Level of Evidence: B)*
3. Either a bioprosthetic or mechanical valve is reasonable in patients between 60 and 70 years of age (259, 260). *(Level of Evidence: B)*

**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)*

### Table 21. Summary of Recommendations for Prosthetic Valve Choice

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice of valve intervention and prosthetic valve type should be a shared decision process</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>A mechanical prosthesis is reasonable for AVR or MVR in patients &lt;60 y of age who do not have a contraindication to anticoagulation</td>
<td>IIa</td>
<td>B</td>
<td>(252-254)</td>
</tr>
<tr>
<td>A bioprosthesis is reasonable in patients &gt;70 y of age</td>
<td>IIa</td>
<td>B</td>
<td>(255-258)</td>
</tr>
<tr>
<td>Either a bioprosthetic or mechanical valve is reasonable in patients between 60 y and 70 y of age</td>
<td>IIa</td>
<td>B</td>
<td>(259, 260)</td>
</tr>
<tr>
<td>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</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.

### 10.2. Antithrombotic Therapy for Prosthetic Valves

**Class I**

1. Anticoagulation with a VKA and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve (261-263). *(Level of Evidence: A)*
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 (264-266). *(Level of Evidence: B)*
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) (267). *(Level of Evidence: B)*
4. Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR (267, 268). *(Level of Evidence: B)*
5. Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (269, 270). *(Level of Evidence: A)*

**Class IIa**

1. Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve (271-274). *(Level of Evidence: B)*
2. Anticoagulation with a VKA is reasonable for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5 (275). *(Level of Evidence: C)*

**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 (276). *(Level of Evidence: B)*
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)*
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 (277-279). (Level of Evidence: B)

10.3. Bridging Therapy for Prosthetic Valves

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)

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)

3. Bridging anticoagulation with either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (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)

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)

10.4. Excessive Anticoagulation and Serious Bleeding With Prosthetic Valves

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 (280, 281). (Level of Evidence: B)

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.

### 10.5. Prosthetic Valve Thrombosis

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

#### 10.5.1. Diagnosis and Follow-Up

**Class I**

1. TTE is indicated in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity and follow resolution of valve dysfunction (282, 283). *Level of Evidence: B*
2. TEE is indicated in patients with suspected prosthetic valve thrombosis to assess thrombus size and valve motion (283-285). *Level of Evidence: B*

**Class IIa**

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

#### 10.5.2. Medical Therapy
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 cm²) (283, 286). *(Level of Evidence: B)*

2. Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves (287, 288). *(Level of Evidence: B)*

10.5.3. Intervention

Class I

1. Emergency surgery is recommended for patients with a thrombosed left-sided prosthetic heart valve with NYHA class III to IV symptoms (287, 289, 290). *(Level of Evidence: B)*

Class IIa

1. Emergency surgery is reasonable for patients with a thrombosed left-sided prosthetic heart valve with a mobile or large thrombus (>0.8 cm²) (283, 285, 290). *(Level of Evidence: C)*

*Figure 7. Evaluation and Management of Suspected Prosthetic Valve Thrombosis*

*See full-text guideline for dosage recommendations.*
Nishimura, RA et al.
2014 AHA/ACC Valvular Heart Disease Guideline

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

10.6. Prosthetic Valve Stenosis

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

10.7. Prosthetic Valve Regurgitation

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 (291, 292). (Level of Evidence: B)

Class IIa
1. Surgery is reasonable for operable patients with severe symptomatic or asymptomatic bioprosthetic regurgitation. (Level of Evidence C)
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 (293-295). (Level of Evidence B)

11. Infective Endocarditis: Recommendations

11.1. Diagnosis and Follow-Up
See Figure 8 for recommendations for imaging studies in native valve endocarditis and prosthetic valve endocarditis.

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 (296) (Level of Evidence: B) or patients with newly diagnosed left-sided valve regurgitation. (Level of Evidence: C)
2. The Modified Duke Criteria should be used in evaluating a patient with suspected IE (Tables 24 and 25 in the full-text guideline) (297-300). (Level of Evidence: B)
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 (301). (Level of Evidence: B)
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 (302-306). (Level of Evidence: B)
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 (307-315). (Level of Evidence: B)
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) (316, 317). *(Level of Evidence: B)*

7. Intraoperative TEE is recommended for patients undergoing valve surgery for IE (318, 319). *(Level of Evidence: B)*

**Class IIa**

1. TEE is reasonable to diagnose possible IE in patients with *Staphylococcal aureus* bacteremia without a known source (320-322). *(Level of Evidence: B)*
2. TEE is reasonable to diagnose IE of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur (323, 324). *(Level of Evidence: B)*
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 (325-328). *(Level of Evidence: B)*

**Class IIb**

1. TEE might be considered to detect concomitant staphylococcal IE in nosocomial *Staphylococcal aureus* bacteremia with a known portal of entry from an extracardiac source (329-331). *(Level of Evidence: B)*

**Figure 8. Recommendations for Imaging Studies in NVE and PVE**

*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.

**11.2. Medical Therapy**

**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 (296). *(Level of Evidence: B)*

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 (332-337). *(Level of Evidence: B)*

Class IIb

1. Temporary discontinuation of VKA anticoagulation might be considered in patients receiving VKA anticoagulation at the time of IE diagnosis (333, 338-341). *(Level of Evidence: B)*

Class III: Harm

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

### 11.3. Intervention

See Figure 9 for diagnosis and treatment of IE.

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 (301). *(Level of Evidence: B)*
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 (342-347). *(Level of Evidence: B)*
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 *Staphylococcal aureus*, fungal, or other highly resistant organisms (347-354). *(Level of Evidence: B)*
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 (347, 355-359). *(Level of Evidence: B)*
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 (347, 352, 353, 360-362). *(Level of Evidence: B)*
6. Surgery is recommended for patients with prosthetic valve endocarditis 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)*
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 (363-366). *(Level of Evidence: B)*

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 *Staphylococcal aureus* or fungi, even without evidence of device or lead infection (363-366). *(Level of Evidence: B)*
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)*
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 (302, 367, 368). *(Level of Evidence: B)*
Class IIb
1. Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered in patients with native valve endocarditis who exhibit mobile vegetations greater than 10 mm in length (with or without clinical evidence of embolic phenomenon) (302, 367, 368). (Level of Evidence: B)

Figure 9. Diagnosis and Treatment of IE

*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.

12. Pregnancy and VHD: Recommendations

12.1. Native Valve Stenosis

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

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*

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*

**12.1.1. Diagnosis and Follow-Up**

**Class IIa**

1. Exercise testing is reasonable in asymptomatic patients with severe AS (aortic velocity ≥4 m per second or mean pressure gradient ≥40 mm Hg, stage C) before pregnancy. *Level of Evidence: C*

**12.1.2. Medical Therapy**

**Class I**

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

**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*

**Class IIb**

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

**Class III: Harm**

1. ACE inhibitors and ARBs should not be given to pregnant patients with valve stenosis (369-371). *Level of Evidence: B*

**12.1.3. Intervention**

**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*

2. Valve intervention is recommended before pregnancy for symptomatic patients with severe MS (mitral valve area ≤1.5 cm², stage D). *Level of Evidence: C*

3. Percutaneous mitral balloon commissurotomy is recommended before pregnancy for asymptomatic patients with severe MS (mitral valve area ≤1.5 cm², stage C) who have valve morphology favorable for percutaneous mitral balloon commissurotomy. *Level of Evidence: C*

**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*
2. Percutaneous mitral balloon commissurotomy is reasonable for pregnant patients with severe MS (mitral valve area \( \leq 1.5 \text{ cm}^2 \), 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 (372-376). \textit{(Level of Evidence: B)}

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

4. Valve intervention is reasonable for pregnant patients with severe AS (mean pressure gradient \( \geq 40 \text{ mm Hg} \), stage D) only if there is hemodynamic deterioration or NYHA class III to IV HF symptoms (377-383). \textit{(Level of Evidence: B)}

Class III: Harm
1. Valve operation should not be performed in pregnant patients with valve stenosis in the absence of severe HF symptoms. \textit{(Level of Evidence: C)}

12.2. Native Valve Regurgitation

12.2.1. Diagnosis and Follow-Up

Class I
1. All patients with suspected valve regurgitation should undergo a clinical evaluation and TTE before pregnancy. \textit{(Level of Evidence: C)}

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. \textit{(Level of Evidence: C)}

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. \textit{(Level of Evidence: C)}

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. \textit{(Level of Evidence: C)}

Class IIa
1. Exercise testing is reasonable in asymptomatic patients with severe valve regurgitation (stage C) before pregnancy. \textit{(Level of Evidence: C)}

12.2.2. Medical Therapy

Class III: Harm
1. ACE inhibitors and ARBs should not be given to pregnant patients with valve regurgitation (369-371). \textit{(Level of Evidence: B)}

12.2.3. Intervention

Class I
1. Valve repair or replacement is recommended before pregnancy for symptomatic women with severe valve regurgitation (stage D). \textit{(Level of Evidence: C)}

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). \textit{(Level of Evidence: C)}
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. \(\text{(Level of Evidence: C)}\)

Class III: Harm
1. Valve operations should not be performed in pregnant patients with valve regurgitation in the absence of severe intractable HF symptoms. \(\text{(Level of Evidence: C)}\)

12.3. Prosthetic Valves in Pregnancy

12.3.1. Diagnosis and Follow-Up

Class I
1. All patients with a prosthetic valve should undergo a clinical evaluation and baseline TTE before pregnancy. \(\text{(Level of Evidence: C)}\)
2. All patients with a prosthetic valve should undergo prepregnancy counseling by a cardiologist with expertise in managing patients with VHD during pregnancy. \(\text{(Level of Evidence: C)}\)
3. TTE should be performed in all pregnant patients with a prosthetic valve if not done before pregnancy. \(\text{(Level of Evidence: C)}\)
4. Repeat TTE should be performed in all pregnant patients with a prosthetic valve who develop symptoms. \(\text{(Level of Evidence: C)}\)
5. TEE should be performed in all pregnant patients with a mechanical prosthetic valve who have prosthetic valve obstruction or experience an embolic event. \(\text{(Level of Evidence: C)}\)
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. \(\text{(Level of Evidence: C)}\)

12.3.2. Medical Therapy
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 (384, 385). \(\text{(Level of Evidence: B)}\)
2. Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimesters (386-391). \(\text{(Level of Evidence: B)}\)
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. \(\text{(Level of Evidence: C)}\)
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. \(\text{(Level of Evidence: C)}\)

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 (384, 385, 390-393). \(\text{(Level of Evidence: B)}\)
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 (386-389, 394, 395). *(Level of Evidence: B)*

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 (384, 385, 392). *(Level of Evidence: B)*

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 (386-389, 394-396). *(Level of Evidence: B)*

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 (384, 385, 392). *(Level of Evidence: B)*

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 (387, 388, 394, 395, 397). *(Level of Evidence: B)*

Figure 10. Anticoagulation of Pregnant Patients With Mechanical Valves
aPTT indicates activated partial thromboplastin time; ASA, aspirin; INR, international normalized ratio; LMWH, low-molecular-weight heparin; QD, once daily; and UFH, unfractionated heparin.
13. Surgical Considerations: Recommendations

13.1. Evaluation of Coronary Anatomy
See Figure 11 for evaluation and management of CAD in patients undergoing valve surgery.

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)
2. Coronary angiography should be performed as part of the evaluation of patients with chronic severe secondary MR. (Level of Evidence: C)

Class IIa
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)
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) can be confirmed with invasive coronary angiography (398-404). (Level of Evidence: B)

13.2. Concomitant Procedures

13.2.1. Intervention for CAD

Class IIa
1. CABG or percutaneous coronary intervention 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)
CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CT, computed tomography; IE, infective endocarditis; LV, left ventricular; and PCI, percutaneous coronary intervention.

13.2.2. Intervention for AF

**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)*
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 (405, 406). *(Level of Evidence: B)*

**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)*
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)*

**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 (407). *(Level of Evidence: B)*

14. Noncardiac Surgery in Patients With VHD: Recommendations

**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 (408-411). *(Level of Evidence: B)*

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)*

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)*

**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)*

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## Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speaker’s Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
<th>Voting Recusals by Section*</th>
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<td>None</td>
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### 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. Section numbers pertain to those in the full-text guideline. †No financial benefit.

AATS indicates American Association of Thoracic Surgery; DSMB, data safety monitoring board; and VA, Veterans Affair.

| James D. Thomas | Cleveland Clinic—Professor of Medicine and Biomedical Engineering | None | None | None | None | None | None | None | 13.1.3, 13.2.1, 13.2.3, 13.3.1, 13.3.2, 14.1, and 14.2.2. |

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Nishimura, RA et al.
2014 AHA/ACC Valvular Heart Disease Guideline
## Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

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* denotes industry support through consulting, advisory boards, speaker bureaus, or research funding in the past 2 years.
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Nishimura, RA et al.
2014 AHA/ACC Valvular Heart Disease Guideline

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Nishimura, RA et al.  
2014 AHA/ACC Valvular Heart Disease Guideline


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2014 Valvular Heart Disease Guideline Data Supplements

Table of Contents
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) ....................... 2
Data Supplement 2. Hemodynamic Progression of Aortic Stenosis in Adult Patients (stages B and C) (Section 3.2.1.3) .......................................................... 5
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) ........................................ 6
Data Supplement 4. Clinical Trials of Lipid Lowering Therapy in Adults With Asymptomatic Mild to Moderate Aortic Stenosis (stage B (Section 3.2.2) ...................... 8
Data Supplement 5. Clinical Outcomes in Asymptomatic Adults With Aortic Stenosis (stages B and C) of Known Hemodynamic Severity (Section 3.2.3) .................. 9
Data Supplement 6. Incidence of Sudden Death in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Section 3.2.3) .................................................. 11
Data Supplement 7. Clinical Outcomes in Symptomatic Adults With Aortic Stenosis of Known Hemodynamic Severity (Section 3.2.3) ........................................ 12
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) ....... 14
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) ............. 16
Data Supplement 10. Clinical Outcomes of Asymptomatic Patients With Chronic Aortic Regurgitation (Sections 4.3.1.1 and 4.3.3) ........................................ 17
Data Supplement 11. Vasodilator Therapy in Asymptomatic Patients With Chronic Aortic Regurgitation (Section 4.3.2) ......................................................... 20
Data Supplement 12. Determinants of Outcome After Surgery for Chronic Aortic Regurgitation (Section 4.3.3) ................................................................. 21
Data Supplement 13. Hemodynamic Effects Percutaneous Mitral Balloon Commissurotomy (PMBC) Compared to Surgical Closed Commissurotomy (CC) or Open Commissurotomy (OC) (Section 6.2.3) ......................................................... 27
Data Supplement 14. Echocardiographic Prediction of Outcome of Percutaneous Balloon Mitral Commissurotomy (Section 6.2.3) ........................................... 28
Data Supplement 15. Randomized Trials of Percutaneous Mitral Balloon Commissurotomy Versus Surgery for Mitral Stenosis (Section 6.2.3) ...................................... 29
Data Supplement 16. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation (Section 7.3.3) ................................................................. 31
Data Supplement 17. Primary Mitral Regurgitation—Evidence for Intervention (Section 7.3.3) ................................................................. 31
Data Supplement 18. Secondary Mitral Regurgitation—Evidence for Intervention (7.4.3) ................................................................. 34
Data Supplement 19. Functional Tricuspid Regurgitation: Outcomes Following Tricuspid Valve Surgery (Sections 8.2.3 and 8.4.3) ........................................... 35
Data Supplement 20. Clinical Outcomes With Bioprosthetic and Mechanical Valves (Section 11.1.2) ................................................................. 37
Data Supplement 21. Bridging Anticoagulation Therapy for Mechanical Heart Valves (Section 11.3.2) ................................................................. 40
Data Supplement 22. Fibrinolytic Therapy for Prosthetic Valve Thrombosis (Section 11.6.2) ................................................................. 42
Data Supplement 23. Paravalvular Regurgitation (Section 11.8.3) ................................................................. 44
Data Supplement 24. Surgical Outcome in Infective Endocarditis (Section 12) ................................................................. 46
Data Supplement 25. Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated With Warfarin or Unfractionated Heparin (UFH) (Section 13.3.2) ............... 51
Data Supplement 26. Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated With Low Molecular Weight Heparin (LMWH) (Section 13.3.2) .......... 54
Data Supplement 27. Outcomes With the Maze Procedure for Atrial Fibrillation in Patients With Valvular Heart Disease (Section 14.2.2) ........................................ 56
Data Supplement 28. Noncardiac Surgery in Patients With Valvular Heart Disease (Section 15.3) ................................................................. 59
References .................................................................................................................. 61
### 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)

<table>
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<th>Study</th>
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<th>Study Type</th>
<th>Study Size</th>
<th>Definition of LFLG Severe AS With lLVEF</th>
<th>Exclusion Criteria</th>
<th>Stress Findings/Clinical Outcomes</th>
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<td>DeFilippi, 1995 (1) 7810504</td>
<td>To determine if DSE can distinguish severe fixed AS from flow-dependent AS</td>
<td>Prospective</td>
<td>24</td>
<td>AVAI ≤0.5 cm²/m² ΔPmean ≤30 mm Hg LVEF ≤45% All symptomatic</td>
<td>Too ill AF</td>
<td>IA. (n=7, 39%) No change in AVA with ≥20% improvement in LVEF (contractile reserve). IB. (n=5, 28%) TAVA ≥0.3 cm² and contractile reserve. II. (n=6, 33%) No contractile reserve.</td>
<td>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.</td>
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<td>Connolly, 1997 (2) 9170402</td>
<td>Determine outcome after AVR for severe AS with LG and low LVEF</td>
<td>Retrospective surgical database</td>
<td>154</td>
<td>LVEF ≤35% Undergoing AVR Other valve disease</td>
<td>Baseline mean AVA 0.6±0.2 cm², Mean cardiac output 4.1±1.5 L/min, Perioperative (30 d) mortality 9%, Postoperative LVEF improved in 76% of pts.</td>
<td>Study group had low LVEF, but not all had LG or LF.</td>
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<tr>
<td>Pereira, 2002 (3) 11955855</td>
<td>Evaluate outcome with AVR vs. medical Rx in LFLG severe AS</td>
<td>Retrospective, propensity score matched</td>
<td>68</td>
<td>AVA ≤0.75 cm² ΔPmean ≤30 mm Hg LVEF ≤35% Other valve disease.</td>
<td>In propensity matched pts, survival at 4 y was 78% with AVR vs.15% with medical Rx (p&lt;0.0001).</td>
<td>Multivariate predictors of survival were AVR, age, and renal function.</td>
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<td>Nishimura, 2002 (4) 12176952</td>
<td>Diagnostic value of invasive hemodynamics with dobutamine stress</td>
<td>Prospective, comparison with surgical findings</td>
<td>32</td>
<td>AVA &lt;1.0 cm² ΔPmean ≤40 mm Hg LVEF &lt;40% N/A</td>
<td>With dobutamine, final AVA ≤1.2 cm² with a ΔPmean &gt;30 mm Hg in 21 pts; severe AS confirmed at surgery. In 15 pts with CR, mortality was 7% (1 death) with medical therapy.</td>
<td>CR defined as ↑SV ≥20% with dobutamine.</td>
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<td>Monin, 2003 (5) 12835219</td>
<td>Assess prognostic value of DSE in LFLG AS</td>
<td>Prospective, multicenter</td>
<td>136</td>
<td>AVA ≤1.0 cm² Cardiac index ≤3 L/min/m² ΔPmean ≤50 mm Hg Other valve disease, severe comorbidities</td>
<td>Operative mortality 5% with CR vs. 32% without CR (p=0.0002). Predictors of long-term survival were AVR and CR.</td>
<td>CR defined as ↑SV ≥20% on DSE.</td>
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<td>Quere, 2006 (6) 16585393</td>
<td>Determine relationship between CR on DSE and postoperative LVEF</td>
<td>Prospective, multicenter</td>
<td>66</td>
<td>AVA ≤1.0 cm² ΔPmean ≤40 mm Hg LVEF ≤40% All symptomatic undergving AVR Excluded operative deaths</td>
<td>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%.</td>
<td>Symptoms improved by ≥2 classes after AVR in 58%. Mean LVEF increased from 29±6% to 47±11% after AVR.</td>
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<td>Blais, 2006 (7) 16461844</td>
<td>Improve differentiation of true from pseudo severe AS on DSE</td>
<td>In vitro model and prospective pt group</td>
<td>23</td>
<td>AVAI ≤0.6 cm²/m² LVEF ≤40% ΔPmean ≤40 mm Hg All symptomatic undergoing AVR Other valve disease AF or paced rhythm</td>
<td>Projected effective orifice area at a normal transvalvular flow rate was accurate for identifying true vs. pseudo severe AS in comparison to surgical findings.</td>
<td>No outcome data.</td>
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<td>Bergler-Klein, 2007 (8) 15117847</td>
<td>Relationship between BNP and outcome in LFLG AS</td>
<td>Prospective, multicenter</td>
<td>69</td>
<td>AVAI &lt;0.6 cm²/m² ΔPmean ≤40 mm Hg LVEF ≤40% Other valve disease, AF, or paced rhythm</td>
<td>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 &lt;550 pg/mL (p=0.0001).</td>
<td>Classified as severe AS if DSE showed AVA ≤1.0 cm² at projected flow rate of 250 mL/s; pseudo-severe if AVA &gt;1.0 cm² projected at 250 mL/s.</td>
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<td>Pai, 2008 (8)</td>
<td>Surgical outcome with low-gradient AS</td>
<td>Retrospective surgical database</td>
<td>362</td>
<td>AVA ≤0.8 cm² AND (\Delta P_{mean} ≤ 30 \text{ mm Hg} ) OR LVEF ≤35%</td>
<td>N/A</td>
<td>In 194 pts with LVEF ≤35%, 5-y survival was 50% with AVR vs. 23% without AVR (p&lt;0.0001). In 168 pts with (\Delta P_{mean} ≤ 30 \text{ mm Hg} ), 5-y survival was 80% with AVR vs. 22% without AVR (p&lt;0.0001).</td>
<td>Univariate predictors of mortality were older age, lower LVEF, renal insufficiency, and lack of AVR.</td>
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<td>Levy, 2008 (10)</td>
<td>Evaluate perioperative mortality with LFLG severe AS</td>
<td>Surgical series AVR for LGFL AS</td>
<td>217</td>
<td>AVA &lt;1 cm² LVEF ≤35% (\Delta P_{mean} ≤ 30 \text{ mm Hg} ) OR LVEF ≤35%</td>
<td>Other valve disease</td>
<td>Perioperative mortality 16% overall (decreased from 20% in 1990s to 10% after 2000). 5-y survival was 49±4%.</td>
<td>Predictors of perioperative mortality were very LG, multivessel CAD, and absence of CR on DSE.</td>
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<td>Clavel, 2010 (11)</td>
<td>Compare outcomes after TAVR vs. SAVR with low LVEF severe AS</td>
<td>Prospective comparison of echo data</td>
<td>200 SAVR; 83 TAVR</td>
<td>AVA ≤1 cm² LVEF ≤60%</td>
<td>No LVEF by echo</td>
<td>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.</td>
<td>Treatment not randomized.</td>
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<td>Tribouilloy, 2009 (12)</td>
<td>Effect of AVR on outcomes in LFLG severe AS without contractile reserve</td>
<td>Prospective, multicenter</td>
<td>81</td>
<td>AVA &lt;1 cm² LVEF ≤40% (\Delta P_{mean} ≤ 40 \text{ mm Hg} ) No contractile reserve</td>
<td>N/A</td>
<td>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).</td>
<td>Contractile reserve defined as ↑SV ≥20% on DSE. Multivariate predictors of mortality were associated bypass surgery (p=0.007) and (\Delta P_{mean} ≤ 20 \text{ mm Hg} ) (p=0.035).</td>
</tr>
<tr>
<td>Gotzmann, 2012 (13)</td>
<td>Outcomes after TAVR with low LVEF and LG AS</td>
<td>Prospective CoreValve TAVR</td>
<td>202</td>
<td>LVEF groups &gt;50% or ≤50% (\Delta P_{mean} ≤ 40 \text{ mm Hg} ) or (\Delta P_{mean} ≤ 30 \text{ mm Hg} ) No contractile reserve</td>
<td>N/A</td>
<td>1-y mortality LVEF &gt;50% 14% (n=88) LVEF ≤50% (\Delta P_{mean} &gt;40 \text{ mm Hg} ) 14% (n=88) (\Delta P_{mean} ≤ 40 \text{ mm Hg} ) 22% (n=27)</td>
<td>1-y mortality after TAVR was higher with LG, lower LVEF severe AS. Severe AS defined as AVA ≤1.0 cm². All pts were high surgical risk.</td>
</tr>
<tr>
<td>Fougeres, 2012 (14)</td>
<td>Outcome of pseudo-severe AS without AVR</td>
<td>Multicenter registry of severe symptomatic LFLG AS</td>
<td>107</td>
<td>AVA ≤ 0.6 cm²/m² LVEF ≤40% (\Delta P_{mean} ≤ 40 \text{ mm Hg} ) Cardiac index ≤3.0 L/min/m²</td>
<td>N/A</td>
<td>IA: 43 true-severe AS IB: 29 with pseudo-severe AS as defined as CR with final AVA ≥1.2 cm² and (\Delta P_{mean} ≤ 40 \text{ mm Hg} ) II: 23 with no CR (TSV &lt;20%)</td>
<td>74 deaths (68%) 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 (\Delta P_{mean} ≤ 20 \text{ mm Hg} ) (HR: 1.55; 95% CI: 1.07–2.23).</td>
</tr>
<tr>
<td>Herrmann, 2013 (15)</td>
<td>Surgical vs. transcatheter AVR for in operable pts with LFLG severe AS with</td>
<td>Subgroup analysis of RCT</td>
<td>42</td>
<td>AVA ≤0.8 cm² or AVAi &lt;0.5 cm²/m² LVEF &lt;50%</td>
<td>N/A</td>
<td>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)</td>
<td>No difference in 2-y outcomes in the 105 pts with LFLG severe AS with low LVEF randomized to SAVR vs.</td>
</tr>
</tbody>
</table>
### Study Aim of Study Study Type Study Size Definition of LFLG Exclusion Criteria Stress Findings/Clinical Outcomes Comments

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size</th>
<th>Definition of LFLG</th>
<th>Exclusion Criteria</th>
<th>Stress Findings/Clinical Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced LVEF</td>
<td>medical Rx</td>
<td>ΔP&lt;sub&gt;mean&lt;/sub&gt; ≤40 mm Hg SVi &lt; 35 mL/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>TAVR (42.9% vs. 37.1%; HR: 1.25, 95% CI: 0.66–2.36; p=0.50).</td>
<td></td>
</tr>
</tbody>
</table>

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<sub>mean</sub>, mean transaortic systolic pressure gradient; pts, adult patients; Rx, prescription; rLVEF, left ventricular reduced ejection fraction; ΔP<sub>mean</sub>, 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.
### Data Supplement 2. Hemodynamic Progression of Aortic Stenosis in Adult Patients (stages B and C) (Section 3.2.1.3)

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>N</th>
<th>Type of Study</th>
<th>Entry Criteria</th>
<th>Mean Follow-up (y)</th>
<th>Increase in ΔP\text{mean} (mmHg/y) (mean± SD)</th>
<th>Increase in V\text{max} (m/s/y) (mean± SD)</th>
<th>Decrease in AVA (cm²/y) (mean± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otto, 1989 (16)</td>
<td>42</td>
<td>Prospective</td>
<td>Asymptomatic; (V_{\text{max}} &gt;2.5) m/s</td>
<td>1.7</td>
<td>8 (-7–23)</td>
<td>0.36±0.31</td>
<td>0.1</td>
</tr>
<tr>
<td>Roger, 1990 (17)</td>
<td>112</td>
<td>Retrospective</td>
<td>AS on echo</td>
<td>2.1</td>
<td>N/A</td>
<td>0.23±0.37</td>
<td>N/A</td>
</tr>
<tr>
<td>Faggiano, 1992 (18)</td>
<td>45</td>
<td>Prospective</td>
<td>AS on echo</td>
<td>1.5</td>
<td>N/A</td>
<td>0.4±0.3</td>
<td>0.1±0.13</td>
</tr>
<tr>
<td>Peter, 1993 (19)</td>
<td>49</td>
<td>Retrospective</td>
<td>AS on echo</td>
<td>2.7</td>
<td>7.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Briner, 1995 (20)</td>
<td>394</td>
<td>Retrospective</td>
<td>AS on echo</td>
<td>6.3</td>
<td>N/A</td>
<td>N/A</td>
<td>0.14</td>
</tr>
<tr>
<td>Otto, 1997 (21)</td>
<td>123</td>
<td>Prospective</td>
<td>Asymptomatic, (V_{\text{max}} &gt;2.5) m/s</td>
<td>2.5</td>
<td>7±7</td>
<td>0.32±0.34</td>
<td>0.12±0.19</td>
</tr>
<tr>
<td>Bahler, 1999 (22)</td>
<td>91</td>
<td>Retrospective</td>
<td>AS on echo</td>
<td>1.8</td>
<td>2.8</td>
<td>0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Falke, 2000 (23)</td>
<td>170</td>
<td>Retrospective</td>
<td>AS on echo</td>
<td>1.9</td>
<td>N/A</td>
<td>N/A</td>
<td>0.10±0.27</td>
</tr>
<tr>
<td>Rosenhek, 2000 (24)</td>
<td>128</td>
<td>Prospective</td>
<td>(V_{\text{max}} &gt;4.0) m/s</td>
<td>1.8</td>
<td>Slow</td>
<td>0.14±0.18</td>
<td>N/A</td>
</tr>
<tr>
<td>Rosenhek, 2004 (25)</td>
<td>176</td>
<td>Retrospective</td>
<td>(V_{\text{max}} 2.5–3.9) m/s</td>
<td>3.8</td>
<td>N/A</td>
<td>0.24±0.30</td>
<td>N/A</td>
</tr>
<tr>
<td>Rossebo, 2008 (26)</td>
<td>1,875</td>
<td>Prospective</td>
<td>(V_{\text{max}} 2.5–4) m/s</td>
<td>4.3</td>
<td>Statin Rx</td>
<td>0.15±0.01</td>
<td>0.03±0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>0.16±0.01</td>
<td>0.03±0.1</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVA, aortic valve area; echo, echocardiography; N/A, not applicable; ΔP\text{mean}, mean transaortic pressure gradient; V\text{max}, maximum velocity.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Exercise Findings/Clinical Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nylander, 1986</td>
<td>Describe hemodynamics, clinical features, noninvasive findings in elderly pts with suspected severe symptomatic AS</td>
<td>Observational, exercise test</td>
<td>76 (37 in NYHA class III/IV)</td>
<td>Suspected symptomatic severe AS, Mean age 65 y</td>
<td>N/A</td>
<td>Inadequate BP increase with exercise in 62%, ETT was at variance with reported NYHA class in 25%. Exercise tolerance was &lt;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.</td>
<td></td>
</tr>
<tr>
<td>Clyne, 1991</td>
<td>Evaluate exercise response</td>
<td>ETT, Thallium perfusion imaging, MUGA</td>
<td>14</td>
<td>Asymptomatic AS</td>
<td>N/A</td>
<td>AS pts had decreased exercise tolerance and VO_{max} vs. controls. ST depression &gt;1 mm flat or downsloping in 71%. Reversible perfusion defect in 21%. ↓BP &gt;10 mm Hg in 7%. No clinical outcome data.</td>
<td></td>
</tr>
<tr>
<td>Otto, 1992</td>
<td>Measure physiologic response to exercise</td>
<td>Prospective, Bruce protocol ETT, Doppler echo</td>
<td>28</td>
<td>Asymptomatic AS</td>
<td>N/A</td>
<td>Exercise duration 6.7±4.3 min V_{max} T3.99±0.93 to 4.61±1.12 m/s (p&lt;0.0001) \triangle P_{mean} T39±20 to 52±26 mm Hg (p&lt;0.0001) Stroke volume ↓3.9±5.29 to 8±3±2 mL (p=0.01) Q_{max} ↑72.2±117 to 523±209 mL/s (p&lt;0.0001) SEP J0 0.33±0.04 to 0.24±0.002 (p&lt;0.0001) Cardiac output ↑7,6±1.7 to 10.2±1.4 L/min (p&lt;0.0001) AVA 1.17±0.45 to 1.28±0.65 (p=NS) \triangle BP &gt;10 mm Hg in 11%. ST depression &gt;1 mm flat or downsloping in 75%. Occasional PVCs in 39%. Asymptomatic 3-beat VT in 4% (1 pt.). No clinical outcome data.</td>
<td></td>
</tr>
<tr>
<td>Otto, 1997</td>
<td>Identify predictors of clinical outcome</td>
<td>Prospective, clinical, echo, and ETT data</td>
<td>104 pts 274 exercise tests</td>
<td>Asymptomatic AS (V_{max}&gt;2.5 m/s)</td>
<td>Unable to walk on treadmill</td>
<td>Univariate predictors of clinical outcome (AVR or death) included a smaller exercise TAVA, BP, and cardiac output ↓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 &gt;10 mm Hg in 9%. ST depression &gt;1 mm flat or downsloping in 69%. ST depression &gt;2 mm flat or downsloping persisting &gt;5 m in recovery in 2%.</td>
<td></td>
</tr>
<tr>
<td>Amato, 2001</td>
<td>To determine prognostic value of exercise testing</td>
<td>Prospective</td>
<td>66 Mean age 49.5 y, 67% men</td>
<td>Severe AS (AVA ≤1.0 cm²)</td>
<td>CAD, arrhythmias, abnormal baseline ECG, comorbid disease</td>
<td>Main outcome measure of sudden death (6%) or symptom onset (52%). Positive ETT in 67%; symptoms in 35%, BP rise &lt;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.</td>
<td></td>
</tr>
<tr>
<td>Alborino, 2002</td>
<td>Risk stratification of asymptomatic pts with</td>
<td>Prospective</td>
<td>30 Mean age</td>
<td>Asymptomatic AS</td>
<td>N/A</td>
<td>Abnormal ETT in 18 (60%) with: Fall in BP (3), angina (1), ECG ST changes (3), dyspnea</td>
<td>At 1 y: All 12 pts with a normal ETT</td>
</tr>
<tr>
<td>Study</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Exercise Findings/Clinical Outcomes</td>
<td>Comments</td>
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</tr>
<tr>
<td>Das, 2005 (32) 15820999</td>
<td>Accuracy of stress testing to predict symptom onset at 12 mo</td>
<td>Prospective</td>
<td>125</td>
<td>Asymptomatic AS AVA &lt;1.4 (mean 0.9±0.2) cm²/m² Normal LVEF</td>
<td></td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Lancellotti, 2005 (33) 16159650</td>
<td>Role of quantitative exercise Doppler</td>
<td>Prospective</td>
<td>69</td>
<td>Asymptomatic AS AVA &lt;1.0 cm²</td>
<td></td>
<td>Abnormal exercise response in 26 (38%) including symptoms, ST depression, failure of BP rise.</td>
<td>Cardiac events (n=18) at 15±7 mo follow-up were predicted by an exercise ↑ΔPmean ≥18 mm Hg, an abnormal exercise test or an AVA &lt;0.75 cm².</td>
</tr>
<tr>
<td>Marechaux, 2010 (34) 20398041</td>
<td>Assess if exercise hemodynamics provide incremental prognostic value to standard ETT data</td>
<td>Prospective, multicenter</td>
<td>186</td>
<td>Moderate-severe AS Normal LV (LVEF ≥50%)</td>
<td></td>
<td>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.</td>
<td>Adverse events associated with age 65 y, diabetes mellitus, LVH, resting ΔPmean 35 mm Hg, exercise ↑ΔPmean &gt;20 mm Hg.</td>
</tr>
<tr>
<td>Rajani, 2010 (35) 11473246</td>
<td>Test if exercise symptoms are due to changes in LV function</td>
<td>Prospective</td>
<td>38</td>
<td>Asymptomatic AVA &lt;1.5 cm²</td>
<td>N/A</td>
<td>ETT revealed symptom in 10 (26%) which was associated with a lower cardiac index, stroke index, and VO₂max compared to those without symptoms.</td>
<td>The only independent predictor of peak cardiac index was the log BNP level (p&lt;0.001; r=0.71)</td>
</tr>
</tbody>
</table>

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; ΔPmean, mean transaortic systolic pressure gradient ; PPV, positive predictive value; pt(s), patients; PVCs, premature ventricular contractions; Qmax, maximum flow rate; SEP, systolic ejection period; VO₂max, maximal oxygen consumption.
### Data Supplement 4. Clinical Trials of Lipid Lowering Therapy in Adults With Asymptomatic Mild to Moderate Aortic Stenosis (stage B (Section 3.2.2))

<table>
<thead>
<tr>
<th>Study Name, First Author, Year</th>
<th>Type of Study, Mean Follow-Up (y)</th>
<th>N</th>
<th>Entry Criteria</th>
<th>Exclusion Criteria</th>
<th>Treatment Group</th>
<th>Serum LDL on Rx (% change from baseline)</th>
<th>Increase in $V_{max}$ (m/s/y) or $\Delta P_{mean}$ (mm Hg/y)</th>
<th>Decrease in AVA (cm²/y)</th>
<th>Other Endpoints</th>
<th>Clinical Endpoints</th>
<th>Study Limitations and Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALTIRE Cowell, 2005 (36)</td>
<td>Randomized, double-blind, Placebo controlled 2.1 y</td>
<td>134</td>
<td>$V_{max} &gt; 2.5$ m/s Aortic valve Ca++ Age &gt; 8 y Asymptomatic</td>
<td>Severe MS, AR, or MR LVEF &lt;35% Statin Rx or indication Cholesterol &lt;150 mg/dL Pacer or ICD Child bearing potential Liver disease Alcohol or drug abuse history</td>
<td>Atorvastatin 80 mg/d (n=77)</td>
<td>63±23 mg/dL (↓53%)</td>
<td>$V_{max}$ 0.2±0.21</td>
<td>0.08±0.11</td>
<td>CT valve Ca++ $\uparrow 22.3\pm21.0$ %/y</td>
<td>Primary endpoints were hemodynamics and valve Ca++</td>
<td>Study drug discontinued in 5% of placebo and 9% of treatment groups. Study not powered for clinical outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=78)</td>
<td>130±30 mg/dL (0%)</td>
<td>0.2±0.21 (p=NS)</td>
<td>0.08±0.11 (p=NS)</td>
<td>CT valve Ca++ $\uparrow 21.7\pm19.8$ %/y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAVE Moura, 2007 (37)</td>
<td>Open-label, prospective. 1.4 y</td>
<td>121</td>
<td>AVA 1.0–1.5 cm² Asymptomatic</td>
<td>CAD, rheumatic mitral valve disease, BAV, liver disease, elevated creatinine, comorbidities</td>
<td>Rosuvastatin 20 mg/d (n=61)</td>
<td>93±21 mg/dL (↓42%)</td>
<td>$V_{max}$ 0.04±0.38</td>
<td>0.05±0.12</td>
<td></td>
<td>Inflammatory markers showed ↓CRP in statin group; ↓IL-6 and ↓sCD40L in both groups</td>
<td>Endpoints were cholesterol levels and AS severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No statin (n=60)</td>
<td>118±29 mg/dL (0%)</td>
<td>0.24±0.30 (p=0.007)</td>
<td>0.1±0.09 (p=0.041)</td>
<td></td>
<td></td>
<td>Pts with LDL &gt;130 mg/dL at baseline were treated, those with LDL &lt;130 received placebo</td>
</tr>
<tr>
<td>ASTRONOMER Chan, 2010 (38)</td>
<td>Randomized, double-blind, Placebo controlled 3.5 y</td>
<td>269</td>
<td>$V_{max}$ 2.5–4.0 m/s Age 18–82 y Asymptomatic</td>
<td>Clinical indication for statin including CAD, CVD, PVD</td>
<td>Rosuvastatin 40 mg/d (n=134)</td>
<td>1.45 mmol/L (↓54%)</td>
<td>$\Delta P_{mean}$ 3.8±4.4</td>
<td>0.06±0.21</td>
<td>7 cardiac deaths 55 AVR</td>
<td>No difference in survival or AVR between groups.</td>
<td>Primary endpoint was AS progression. Composite clinical outcome was secondary outcome.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Placebo (n=135)</td>
<td>1.61 mmol/L (↑1.8%)</td>
<td>3.9 ±4.9 (p=NS)</td>
<td>0.07±0.15 (p=NS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEAS Rossebø, 2008 (26)</td>
<td>Randomized, double-blind, Placebo controlled 5.4 y</td>
<td>1,873</td>
<td>$V_{max}$ 2.5–4.0 m/s Age 45–85 y Asymptomatic</td>
<td>CAD, PVD, CVD, DM Clinical indication for statin</td>
<td>Simvastatin 40 mg plus ezetimibe 10 mg/d (n=944)</td>
<td>53±23 mg/dL (↓61%)</td>
<td>$V_{max}$ 0.15±0.01</td>
<td>0.03±0.01</td>
<td>333 composite outcome of CV death, AVR, CHF, and CAD events</td>
<td>No difference for aortic valve related events HR: 1.00; 95% CI: 0.84–1.18</td>
<td>Noncardiac deaths occurred in 5.9% of treatment group and 4.7% of placebo group (p=0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=929)</td>
<td>139±35 mg/dL (0%)</td>
<td>0.16±0.01 (p=NS)</td>
<td>0.03±0.01</td>
<td>333 composite outcome (p=NS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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; $\Delta P_{mean}$, mean transaortic systolic pressure gradient; PVD, peripheral vascular disease; pt(s), patient(s); Rx, prescription; sCD40L, soluble CD40 ligand; $V_{max}$, maximum transvalvular aortic velocity.
### Data Supplement 5. Clinical Outcomes in Asymptomatic Adults With Aortic Stenosis (stages B and C) of Known Hemodynamic Severity (Section 3.2.3)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Size (N)</th>
<th>Patient Population Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Pt. Age (y)</th>
<th>% Male</th>
<th>Follow-Up (mo)</th>
<th>AS Severity at Entry</th>
<th>Event-Free Survival</th>
<th>Cardiac Events</th>
<th>Multivariate Predictors of Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly, 1988 (39)</td>
<td>51</td>
<td>V\textsubscript{max} ≥3.5 m/s Asymptomatic</td>
<td>Other valve disease</td>
<td>63±19</td>
<td>75%</td>
<td>17±0</td>
<td>ΔP 68±19 mm Hg</td>
<td>60% at 2 y</td>
<td>21 AS symptom onset 8 deaths (2 cardiac)</td>
<td>N/A</td>
</tr>
<tr>
<td>Pellikka, 1990 (40)</td>
<td>113</td>
<td>V\textsubscript{max} ≥4.0 m/s Age≥40 y Asymptomatic</td>
<td>Other valve disease CAD Prior valve procedure Early aortic intervention</td>
<td>70 (40–94)</td>
<td>67%</td>
<td>20</td>
<td>V\textsubscript{max} 4.3 (4–6) m/s</td>
<td>62% at 2 y</td>
<td>37 AS symptoms (20 with AVR) 14 deaths (6 cardiac)</td>
<td>V\textsubscript{max} ≥4.5 m/s; RR: 4.9 (1.64–14.6) LVEF &lt;50%; RR: 2.93 (0.84–10.2)</td>
</tr>
<tr>
<td>Kennedy, 1991 (41)</td>
<td>66</td>
<td>AVA 0.7–1.2 cm\textsuperscript{2} at cath</td>
<td>Other valve disease Previous valve surgery</td>
<td>67±10</td>
<td>77%</td>
<td>35</td>
<td>AVA 0.92±0.13 cm\textsuperscript{2}</td>
<td>59% at 4 y</td>
<td>21 AVR (13 for symptoms) 14 deaths due to AS</td>
<td>AVA HR: 0.33 for a 1 cm\textsuperscript{2} increase (95%CI: 0.15–0.71). LVH by ECG HR: 1.39 (95% CI: 1.02–1.89).</td>
</tr>
<tr>
<td>Otto, 1997 (21)</td>
<td>123</td>
<td>V\textsubscript{max} ≥2.6 m/s Asymptomatic</td>
<td>Severe comorbid disease</td>
<td>63±16</td>
<td>70%</td>
<td>30</td>
<td>V\textsubscript{max} &lt;3 m/s V\textsubscript{max} 3–4 m/s V\textsubscript{max} &gt;4 m/s</td>
<td>84% at 2 y 66% at 2 y 21% at 2 y</td>
<td>48 AVR for symptoms 8 deaths</td>
<td>V\textsubscript{max} Functional status score Rate of change in V\textsubscript{max}</td>
</tr>
<tr>
<td>Rosenhek, 2000 (24)</td>
<td>128</td>
<td>V\textsubscript{max} ≥4.0 m/s Asymptomatic</td>
<td>Other valve disease</td>
<td>60±18</td>
<td>54%</td>
<td>22±18</td>
<td>V\textsubscript{max} 5.0±0.7 m/s</td>
<td>67% at 1 y 56% at 2 y 33% at 4 y</td>
<td>59 AVF for symptoms 8 deaths</td>
<td>Extent of valve calcification RR: 4.6 (1.6–14.0).</td>
</tr>
<tr>
<td>Rosenhek, 2004 (25)</td>
<td>176</td>
<td>V\textsubscript{max} 2.5–3.9 m/s LVEF &gt;50% No AS symptoms</td>
<td>Other valve disease</td>
<td>58±19</td>
<td>59%</td>
<td>48±19</td>
<td>V\textsubscript{max} 3.1±0.4 m/s</td>
<td>95% at 1 y 75% at 2 y 60% at 5 y</td>
<td>33 AVF for symptoms 34 deaths</td>
<td>Severe valve calcification RR: 2.0 (1.3–3.3). V\textsubscript{max} ≥3 m/s RR: 1.6 (1.04–2.8). CAD RR: 1.7 (1.2–2.7).</td>
</tr>
<tr>
<td>Pellikka, 2005 (42)</td>
<td>622</td>
<td>V\textsubscript{max} ≥4.0 m/s No AS symptoms</td>
<td>Other valve disease CAD</td>
<td>72±11</td>
<td>62%</td>
<td>65±48</td>
<td>V\textsubscript{max} 4.4 ±0.4 m/s</td>
<td>82% at 1 y 67% at 2 y 33% at 5 y</td>
<td>297 AS symptoms (AVR in 207 of these) 103 deaths without AVR or AS symptoms</td>
<td>AVA HR: 0.33 for a 1 cm\textsuperscript{2} increase (95%CI: 0.15–0.71). LVH by ECG HR: 1.39 (95% CI: 1.02–1.89).</td>
</tr>
<tr>
<td>Rossebo, 2008 (26)</td>
<td>1,873</td>
<td>V\textsubscript{max} 2.5 m/s to 4.0 m/s CAD, CHF, diabetes mellitus, CVA, PVD, and other valve disease</td>
<td>No AS symptoms LVEF ≥55%</td>
<td>68±9</td>
<td>59%</td>
<td>52 (median)</td>
<td>V\textsubscript{max} 3.1±0.55</td>
<td>65% at 5 y</td>
<td>668 (36%) Major CV events (death, AVR, CHF, coronary events, and ischemic stroke)</td>
<td>No effect of statin therapy on major CV events.</td>
</tr>
<tr>
<td>Lancellotti, 2010 (43)</td>
<td>163</td>
<td>AVA ≤0.6 cm\textsuperscript{2}/m\textsuperscript{2} No AS symptoms LVEF ≥55%</td>
<td>Nonsinus rhythm Other valve disease</td>
<td>70±10</td>
<td>65%</td>
<td>20±19</td>
<td>≤0.6 cm\textsuperscript{2}/m\textsuperscript{2}</td>
<td>50% at 2 y 44% at 4 y</td>
<td>11 symptoms, but no AVR 57 AVR 6 deaths</td>
<td>V\textsubscript{max} ≥4.4 m/s, LV longitudinal deformation ≤15.5%, valvulo-arterial impedance ≥4.8 mm Hg/m\textsuperscript{2}, LA area</td>
</tr>
</tbody>
</table>
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Size (N)</th>
<th>Patient Population Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Pt. Age (y)</th>
<th>% Male</th>
<th>Follow-Up (mo)</th>
<th>AS Severity at Entry</th>
<th>Event-Free Survival</th>
<th>Cardiac Events</th>
<th>Multivariate Predictors of Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, 2010 (44) 20308614</td>
<td>95</td>
<td>AVA &gt;0.75 cm² plus Vₘₚ ≥4.5 m/s or ΔPₑₘₑ ≥50 mm Hg</td>
<td>No AS symptoms</td>
<td>63±12</td>
<td>46%</td>
<td>50</td>
<td>Vₑₘₑ 4.9±0.4</td>
<td>71±5% at 2 y</td>
<td>18 cardiac deaths</td>
<td>Vₑₘₑ ≥12.2 cm²/m²</td>
</tr>
<tr>
<td>Stewart, 2010 (45) 20513730</td>
<td>183</td>
<td>Vₑₘₑ &gt;3 m/s</td>
<td>LVHF, AS severity ≥50%</td>
<td>70</td>
<td>65%</td>
<td>31 (median)</td>
<td>AVA 0.81 (IQR: 0.62–1.01) cm²</td>
<td>Probability of symptom free survival at 3 y (95% CI)</td>
<td>103 AS symptoms</td>
<td>Vₑₘₑ ≥12.2 cm²/m²</td>
</tr>
<tr>
<td>Rosenhek, 2010 (46) 20262771</td>
<td>116</td>
<td>Vₑₘₑ ≥5.0 m/s</td>
<td>No AS symptoms</td>
<td>67±15</td>
<td>49%</td>
<td>41 (median)</td>
<td>Vₑₘₑ 5.0–5.5 m/s</td>
<td>43% at 2 y</td>
<td>90 AVR</td>
<td>Vₑₘₑ, but not AVA predicted outcome</td>
</tr>
<tr>
<td>Jander, 2011 (47) 21321152</td>
<td>435</td>
<td>Low gradient &quot;severe&quot; AS: AVA &lt;1 cm² with ΔPₑₘₑ ≤40 mm Hg</td>
<td>CAD, CHF, diabetes, CVA, PVD, and other valve disease</td>
<td>70±9</td>
<td>45%</td>
<td>46±14</td>
<td>Vₑₘₑ 3.3±0.5 m/s</td>
<td>No difference in event rates between groups</td>
<td>183 AVR</td>
<td>Low gradient &quot;severe&quot; AS defined as an AVA &lt;1 cm² with ΔPₑₘₑ ≤40 mm Hg was NOT a predictor of clinical outcome</td>
</tr>
<tr>
<td>Salto, 2012 (48) 22497679</td>
<td>103</td>
<td>AVA &lt;1.0 cm²</td>
<td>No AS symptoms</td>
<td>72±11</td>
<td>45%</td>
<td>36±27</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>41% at 3 y</td>
<td>31 AVR</td>
<td>AVA &lt;0.6 cm²/m² (HR: 2.6; 95% CI: 11.1–6.3), Vₑₘₑ &gt;4.0 m/s (HR: 2.6; 95% CI: 1.2–5.8), (AVA&lt;0.75 cm² did not predict outcome)</td>
</tr>
</tbody>
</table>

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; ΔPₑₘₑ, mean transaortic systolic pressure gradient; pt(s), patient(s); PVD, peripheral vascular disease; RR, relative risk; SEAS, Simvastatin Ezetimibe in Aortic Stenosis study; Vₑₘₑ, maximum velocity.
### 2014 Valvular Heart Disease Guideline Data Supplements

#### Data Supplement 6. Incidence of Sudden Death in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Section 3.2.3)

<table>
<thead>
<tr>
<th>First Author</th>
<th>N</th>
<th>Follow-Up (mo)*</th>
<th>V_{\text{max}} \text{ at Entry (m/s)}</th>
<th>AVA at Entry (cm}^2)</th>
<th>Sudden Deaths (n)</th>
<th>Sudden Deaths (% per y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly, 1988 (39)</td>
<td>51</td>
<td>18</td>
<td>≥3.5</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Faggiano, 1992 (18)</td>
<td>37</td>
<td>24</td>
<td>N/A</td>
<td>0.85±0.15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otto, 1997 (21)</td>
<td>114</td>
<td>30</td>
<td>3.6±0.6</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rosenhek, 2000 (24)</td>
<td>128</td>
<td>22</td>
<td>≥4.0</td>
<td>N/A</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Amato, 2001(30)</td>
<td>66</td>
<td>15</td>
<td>N/A</td>
<td>≤1.0</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Das, 2005 (32)</td>
<td>125</td>
<td>12</td>
<td>N/A</td>
<td>≤1.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pellikka, 2005 (42)</td>
<td>270</td>
<td>65</td>
<td>≥4.0</td>
<td>N/A</td>
<td>11</td>
<td>0.75</td>
</tr>
<tr>
<td>Rosseba, 2008 (26)</td>
<td>1,873</td>
<td>52</td>
<td>2.3–4.0</td>
<td>N/A</td>
<td>40</td>
<td>0.5</td>
</tr>
<tr>
<td>Monin, 2009 (49)</td>
<td>211</td>
<td>22</td>
<td>≥3.0</td>
<td>≤1.5</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Lancellotti, 2010 (43)</td>
<td>163</td>
<td>20</td>
<td>N/A</td>
<td>≤0.6 cm²/m²</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Kang, 2010 (44)</td>
<td>95</td>
<td>59</td>
<td>≥4.5</td>
<td>≥0.75</td>
<td>9</td>
<td>1.9</td>
</tr>
<tr>
<td>Marechaux, 2010 (34)</td>
<td>135</td>
<td>20</td>
<td>N/A</td>
<td>≤1.5</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Rosenhek, 2010 (46)</td>
<td>116</td>
<td>41</td>
<td>≥5.0</td>
<td>N/A</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>3,384</td>
<td>31*</td>
<td>N/A</td>
<td>N/A</td>
<td>72</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Mean follow-up duration.
AVA indicates aortic valve area; N/A, not applicable; and V_{\text{max}}, maximum aortic velocity

From Rosenhek R et al., (50). (PERMISSION NEEDED)
## 2014 Valvular Heart Disease Guideline Data Supplements

### Data Supplement 7. Clinical Outcomes in Symptomatic Adults With Aortic Stenosis of Known Hemodynamic Severity (Section 3.2.3)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Predictors of Mortality or AVR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank, 1973 (51) 4685905</td>
<td>Outcomes with AS of known hemodynamic severity</td>
<td>Observational</td>
<td>15</td>
<td>Isolated AS. Not referred for AVR</td>
<td>Symptomatic (10) or asymptomatic (5) No other valve disease</td>
<td>Mortality from symptom onset: 15% at 2 y 30% at 3 y 52% at 5 y 90% at 10 y</td>
<td>Overlap in hemodynamic parameters between 5 asymptomatic and 10 symptomatic pts</td>
</tr>
<tr>
<td>Chizner, 1980 (52) 7199084</td>
<td>Outcomes with AS of known hemodynamic severity</td>
<td>Observational</td>
<td>32</td>
<td>Symptomatic AS Not referred for AVR</td>
<td>Mortality from symptom onset: 25% at 1 y 57% by 3 y 64% by 5 y 80% by 8 y</td>
<td>Mortality was no different with “moderate” (AVA 0.71–1.1 cm², peak ΔP &lt;70 mm Hg) compared to “severe” AS (AVA 0.7 cm², peak ΔP &gt;70 mm Hg).</td>
<td>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</td>
</tr>
<tr>
<td>Lombard &amp; Selzer, 1987 (53) 3800187</td>
<td>Describe clinical findings in pts with AS of known hemodynamic severity</td>
<td>Retrospective</td>
<td>397</td>
<td>Undergoing cardiac cath for AS</td>
<td>Early symptoms (angina and syncope) correlated with AS severity, but not LV function. Late symptoms (HF) correlated with LV dysfunction.</td>
<td>N/A</td>
<td>No outcome data</td>
</tr>
<tr>
<td>Turina, 1987 (54) 3609042</td>
<td>Determine prognostic value of hemodynamic and clinical variables</td>
<td>Observational</td>
<td>N/A</td>
<td>Referred for cardiac cath. No AVR due to disease severity or pt refusal</td>
<td>Survival without AVR by AS severity: Severe AS (AVA &lt;0.9 cm²): 60% at 1 y, 9% at 10 y Moderate AS (AVA 0.95–1.4 cm²): 97% at 1 y, 35% at 10 y Mild AS (AVA &gt;1.5 cm²): 85% at 10 y</td>
<td>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</td>
<td>AS was more severe in severely symptomatic vs. oligosymptomatic pts: ΔPmean 69 vs. 57 mm Hg (p=NS), AVA 0.56 vs. 0.76 cm² (&lt;0.01), Cardiac index 2.8 vs. 3.3 L/min/m² (p&lt;0.01), LVEDP 17 mm Hg vs.12 mm Hg (p&lt;0.05).</td>
</tr>
<tr>
<td>Horskotte, 1988 (55) 3042404</td>
<td>Compare outcomes with symptomatic vs. asymptomatic severe AS</td>
<td>Retrospective</td>
<td>35</td>
<td>Severe symptomatic AS Refused AVR. AVA 0.4–0.8 cm²</td>
<td>Mean interval from symptom onset to death: 4.5 y for angina (n=10) 2.6 y for syncope (n=13) &lt;1 y for HF (n=20)</td>
<td>Mortality reached 100% at: 10 y for angina 5 y for syncope 2.4 y for HF</td>
<td>There were 3 sudden deaths before symptom onset</td>
</tr>
<tr>
<td>Kelly, 1988 (39) 3337000</td>
<td>Compare outcomes with symptomatic vs. asymptomatic severe AS</td>
<td>Prospective</td>
<td>39</td>
<td>Referred for echo for systolic murmur with Doppler ΔP ≥50 mm Hg cardiac symptoms, but did not undergo AVR. No other valve disease.</td>
<td>Death in 15 (38%) with a mean follow-up of 12 mo. Compared to 8 (%) deaths in 51 initially asymptomatic pts (See Table 6).</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Size (N)</td>
<td>Patient Population</td>
<td>Primary Endpoint</td>
<td>Predictors of Mortality or AVR</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Otto, 1988 (56) 3143323</td>
<td>Identify echo criteria for AVR with symptomatic AS</td>
<td>Prospective, split sample decision analysis</td>
<td>103</td>
<td>Symptomatic pts undergoing cardiac cath for suspected AS</td>
<td>Decision model recommended AVR in 73 with: $V_{max} &gt;4.0$ m/s, or $V_{max} 3.0-4.0$ m/s and AVA&lt;1.0 cm$^2$ or $V_{max} 3.0-4.0$ m/s, AVA &gt;1.0 and 2-3+AR</td>
<td>AVR in 68, 2 noncardiac death, 2 nonsurgical candidates, 1 refused</td>
<td>No difference in Doppler AS severity between these 39 symptomatic and 51 asymptomatic pts during the same time interval. Overall diagnostic accuracy for clinical outcome 94%</td>
</tr>
<tr>
<td>Oh, 1988 (57) 3366997</td>
<td>Compare echo and cath data</td>
<td>Prospective</td>
<td>100</td>
<td>Symptomatic AS undergoing cardiac cath</td>
<td>Severe AS at cath defined as (Gorlin AVA &lt;0.75 cm$^2$)</td>
<td>No outcome data</td>
<td>$V_{max} &gt;4.5$ m/s predicted severe AS at cath with 60% accuracy–specificity 93%, but sensitivity 44% Doppler velocity ratio &lt;0.25 had sensitivity of 92% for severe AS</td>
</tr>
<tr>
<td>Galan, 1991 (58) 2018003</td>
<td>Identify echo predictors of AVR</td>
<td>Observational, retrospective</td>
<td>510</td>
<td>Consecutive AS pts undergoing Doppler echo</td>
<td>Comparison with diagnosis of critical AS at cath, defined as Gorlin AVA &lt;0.75 cm$^2$</td>
<td>In 160 pts with $V_{max} &gt;4.5$ m/s or Doppler AVA &lt;0.75 cm$^2$, 109 underwent AVR No long-term outcome data</td>
<td>$V_{max} &gt;4.5$ m/s or Doppler AVA &lt;0.75 cm$^2$ was 97% specific for critical AS at cath (n=105) $V_{max} &lt;4.5$ m/s or Doppler AVA &gt;0.75 cm$^2$ was 95% specific for noncritical AS at cath (n=133)</td>
</tr>
<tr>
<td>Otto, 1994 (59) 8313553</td>
<td>Outcomes after aortic balloon dilation</td>
<td>Registry</td>
<td>874</td>
<td>Severe symptomatic AS undergoing aortic balloon dilation $V_{max} 4.4 \pm 0.8$ (2.3–6.6) m/s AVA 0.6 ±0.2 (0.1–1.4) cm$^2$</td>
<td>Overall survival was 55% at 1 y, 35% at 2 y, and 23% at 3 y, with 70% of deaths classified as cardiac</td>
<td>Multivariate predictors of outcome were functional status, LV systolic function, renal function, sex, cardiac output, and MR</td>
<td>All pts underwent aortic balloon dilation in this registry so outcomes may be worse with no intervention.</td>
</tr>
</tbody>
</table>

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; $\Delta P_{mean}$, mean transaortic systolic pressure gradient; pt(s), patient(s); and $V_{max}$, maximum velocity.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size</th>
<th>Definition of LFLG severe AS</th>
<th>Exclusion Criteria</th>
<th>Clinical Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hachicha, 2007 (60) 17533183</td>
<td>Determine prevalence, mechanisms and clinical relevant of LFLG severe AS with pLVEF</td>
<td>Retrospective, consecutive pts with severe AS (AVA ≤0.6 cm² and LVEF ≥50%)</td>
<td>512 pts, mean age 70±14 y, 43% women</td>
<td>181 (35%) LFLG severe AS pLVEF: SVi ≤35 mL/m² and AVA ≤0.6 cm² and LVEF≥50%</td>
<td>LVEF &lt;50%</td>
<td>76% survival at 3 y with LFLG severe AS 86% survival at 3 y with normal flow severe AS (p=0.006)</td>
<td>In LFLG severe AS group: Average BSA 1.8±0.2 m² Average AVA 0.76±0.23 cm² Average Vmax 3.5±0.9 m/s LFLG severe AS typically associated with small LV with restrictive physiology</td>
</tr>
<tr>
<td>Jander, 2011 (47) 21321152</td>
<td>Evaluate outcome of LG severe AS</td>
<td>Prospective (SEAS substudy)</td>
<td>435 with LG severe AS vs. 184 with moderate AS</td>
<td>AVA &lt;1.0 cm² and ΔPmean ≤40 mm Hg (Moderate AS defined as AVA 1.0–1.5 cm², ΔPmean 25–40 mm Hg)</td>
<td>See SEAS study in Table 4</td>
<td>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)</td>
<td>In 223 pts with LFLG severe AS pLVEF (SVi ≤35 mL/m²) aortic valve events were no different compared to pts with a normal SVi (46.2% vs. 50.9%; p=0.53).</td>
</tr>
<tr>
<td>Tarantini, 2011 (61) 21619977</td>
<td>Investigate outcome after AVR for LFLG severe AS with pLVEF</td>
<td>Retrospective surgical series</td>
<td>73 AVR 29 medical Rx</td>
<td>AVA ≤1.0 cm² and LVEF &gt;50%</td>
<td>Age &lt;18 y Other valve disease Previous valve surgery</td>
<td>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 cm².</td>
<td>Low SVi present in 20 (27%) AVR and 6 (21%) medical Rx pts with no difference in outcome for normal vs. low SVi</td>
</tr>
<tr>
<td>Clavel, 2012 (62) 22657269</td>
<td>Compare outcome in AS with normal LVEF with 1) LFLG severe AS, 2) high mean gradient (&gt;40 mm Hg) severe AS, and 3) moderate AS (AVA &gt;1.0 cm²)</td>
<td>Case match study</td>
<td>187 with LFLG severe AS matched to 187 moderate AS and 187 high-flow severe AS</td>
<td>ΔPmean &lt;40 mm Hg SVi &lt;35 mL/m² and AVA ≤1.0 cm²</td>
<td>Survival at 1 and 5 y: LFLG severe AS pLVEF 64±4% High-gradient severe AS 96±1% and Moderate AS 81±3%</td>
<td>AVR associated with improved survival for high-gradient severe AS (HR: 0.18; p=0.001) and LFLG severe AS pLVEF in 5% of pts</td>
<td></td>
</tr>
<tr>
<td>Lancellotti, 2012 (63) 22240128</td>
<td>Evaluate clinical course in AS pts stratified by SVi and ΔPmean</td>
<td>Prospective</td>
<td>150 consecutive pts with asymptomatic severe AS (AVA &lt;1.0 cm²) referred for ETT</td>
<td>LVEF &lt;55%, other valve disease, AS, pulmonary disease, inability to exercise</td>
<td>Event free survival at 2 y (p&lt;0.0001): Normal flow (SVi ≥35 mL/m²) 83±6% (n=78) Low-flow (SVi &lt;35 mL/m²) 27±13% (n=11)</td>
<td>Predefined endpoints were CV death in 6 and AVR in 70 pts</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Size</td>
<td>Definition of LFLG severe AS</td>
<td>Exclusion Criteria</td>
<td>Clinical Outcomes</td>
<td>Comments</td>
</tr>
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<tr>
<td>Herrmann 2013 (15) 23661722</td>
<td>Evaluate outcomes with TAVR compared to medical therapy with LG severe AS</td>
<td>Subgroup analysis of RCT</td>
<td>52 inoperable symptomatic pts with LFLG severe AS with normal LVEF</td>
<td>ΔPmean &lt;40 mm Hg SV:&lt;35 mL/m² and AVA &lt;0.8 cm² or AVAi &lt;0.5 cm²/m²</td>
<td>LVEF &lt;50%</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>Le Ven 2013 (64) 23770192</td>
<td>Evaluate effect of LV EF and gradient on outcomes after TAVR</td>
<td>Retrospective analysis of registry data</td>
<td>639 severe AS undergoing TAVR</td>
<td>Low flow (SVi &lt;35 mL/m²) with a normal EF (&gt;50%) was present in 86 (13%) of pts</td>
<td>---</td>
<td>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/m² SVi decrease, p=0.016), and cumulative cardiovascular mortality (hazard ratio: 1.29 per 10 mL/m² decrease, p=0.04).</td>
<td></td>
</tr>
<tr>
<td>Mehrotra 2013 (65) 23533186</td>
<td>Compare clinical characteristics and outcomes in AS subgroups</td>
<td>Retrospective echocardiographic database</td>
<td>LFLG severe AS in 38 pts, compared to 75 normal flow low gradient and 70 moderate AS pts.</td>
<td>AVA ≤1.0 cm² with LVEF≥ 55%, mean gradient &lt;40 mm Hg and SVi &lt;35 mL/m².</td>
<td>Mitral valve disease, aortic regurgitation, poor quality study. Severe AS with mean gradient &gt;40 mm Hg.</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>Ozkan 2013 (66) 23812184</td>
<td>Compare outcomes of LG severe AS with AVR or medical therapy</td>
<td>Prospective follow-up of symptomatic severe LG AS</td>
<td>260 pts with symptomatic severe AS (AVAi ≤0.6 cm²/m²) and mean gradient &lt;40 mm Hg</td>
<td>Normal flow present in 125; low flow (SVi ≤35 mL/m²) in 135.</td>
<td>Mitral disease, aortic regurgitation</td>
<td>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 &gt;35 mL/m²; p=0.22).</td>
<td></td>
</tr>
<tr>
<td>Eleid 2013 (67) 24048203</td>
<td>Evaluate impact of stroke volume with normal EF on outcomes with severe AS</td>
<td>Echocardiographic database.</td>
<td>1,704 consecutive pts with severe AS (AVA &lt;1.0 cm²) and LVEF≥50%</td>
<td>Low flow = SVi ≤35 mL/m² Low gradient &lt;40 mm Hg LFLG present in 53 pts (3%) compared to normal flow LG (n=352, 21%) and to high gradient severe AS.</td>
<td>Prosthetic valve, congenital or other native valve disease</td>
<td>AVR was associated with a 69% mortality reduction (HR 0.31 (0.25, 0.39) p&lt;0.0001) in LF/LG and NF/HG, with no survival benefit associated with AVR in NF/LG and LF/HG.</td>
<td></td>
</tr>
</tbody>
</table>

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; ΔPmean, 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 Vmax, maximum velocity.
### 2014 Valvular Heart Disease Guideline Data Supplements

**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)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Groups (N)</th>
<th>Patient Population</th>
<th>Major Endpoints</th>
<th>Other Results</th>
</tr>
</thead>
</table>
| 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                                    | Severe symptomatic calcific AS defined as AVA <0.8 cm² 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 3.4% vs. SAVR 6.5%  
1 y* 24.2% vs. 26.8%  
2 y 33.9% vs. 35.0%  
(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) 20951243 | 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 cm² 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. 5.3% (p=0.01)  
Major vascular complications occurred in 16.2% with TAVR vs. 11.1% 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)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Mean Follow-Up (y)</th>
<th>Inclusion Criteria, Details</th>
<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
</table>
| 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 7±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 |
| Siemenczuk, 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  
Endpoints: death, symptoms, subnormal LV fractional shortening | 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) |
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Mean Follow-Up (y)</th>
<th>Inclusion Criteria, Details</th>
<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tornos, 1995 (77) 7631617</td>
<td>Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>Prospective, observational series; consecutive pts beginning in 1982; single institution</td>
<td>101</td>
<td>4.6</td>
<td>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</td>
<td>No pt died Progression to symptoms or LV dysfunction: 3.0%/y Progression to asymptomatic LV dysfunction: 1.3%/y</td>
<td>Outcome associated with pulse pressure, LVESD, LVEDD, and LVEF at rest Initial LVESD &gt;50 mm was associated with risk of death, symptoms, and/or LV dysfunction of 7% per y</td>
</tr>
<tr>
<td>Ishii, 1996 (78) 8798222</td>
<td>Clinical outcome and LV response to chronic AR</td>
<td>Prospective, observational series; consecutive pts 1970-1990; single institution</td>
<td>27</td>
<td>14.2</td>
<td>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</td>
<td>No pt died Progression to symptoms or LV dysfunction: 3.6%/y</td>
<td>Development of symptoms associated with systolic BP, LVESD, LVEDD, mass index, and wall thickness. LV function not reported in all pts</td>
</tr>
<tr>
<td>Borer, 1998 (79) 9494022</td>
<td>Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>Prospective, observational series; consecutive pts beginning in 1979; single institution</td>
<td>104</td>
<td>7.3</td>
<td>Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 42±15 y 20% of pts in NYHA II initially Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction</td>
<td>4 pts died suddenly Progression to symptoms or LV dysfunction: 6.2%/y Progression to asymptomatic LV dysfunction: 0.9%/y</td>
<td>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</td>
</tr>
<tr>
<td>Tarasoutchi, 2003 (80) 12706927</td>
<td>Clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>Prospective, observational series; consecutive pts beginning in 1979; single institution</td>
<td>72</td>
<td>10</td>
<td>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</td>
<td>No pt died Progression to symptoms or LV dysfunction: 4.7%/y Progression to asymptomatic LV dysfunction: 0.1%/y</td>
<td>AR of predominant rheumatic etiology LV function not reported in all pts Development of symptoms associated with LVESD and LVEDD Initial LVESD &gt;50 mm was associated with risk of symptoms and/or LV dysfunction of 7.6%/y</td>
</tr>
<tr>
<td>Evangelista, 2005 (81) 16192479</td>
<td>Effect of nifedipine versus enalapril on outcomes of pts with severe AR and normal LV function</td>
<td>Randomized clinical drug trial (see Data Supplement 11); single institution</td>
<td>31</td>
<td>7</td>
<td>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</td>
<td>1 pt died from HF Progression to death, symptoms or LV dysfunction: 3.6%/y</td>
<td>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)</td>
</tr>
<tr>
<td>Study, Year</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Size (n)</td>
<td>Mean Follow-Up (y)</td>
<td>Inclusion Criteria, Details</td>
<td>Outcomes</td>
<td>Comments, Limitations</td>
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<tr>
<td>Detaint, 2008</td>
<td>Predictive value of quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution</td>
<td>251</td>
<td>8</td>
<td>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</td>
<td>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%</td>
<td>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 &lt;50 y in this series</td>
</tr>
<tr>
<td>Pizzaro, 2011</td>
<td>Predictive value of BNP and quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution</td>
<td>294</td>
<td>3.5</td>
<td>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</td>
<td>5 pts died Progression to symptoms or LV dysfunction: 10%/y Progression to asymptomatic LV dysfunction: 2.8%/y</td>
<td>Outcome associated with BNP &gt;130 pg/mL Outcome also associated with RV, ROA, LVEDS index, LVEDD index, ESV index, and EVD index</td>
</tr>
<tr>
<td>Olsen, 2011</td>
<td>Predictive value of speckle-tracking echo in asymptomatic pts with chronic AR and normal LV systolic function</td>
<td>N/A</td>
<td>35</td>
<td>1.6</td>
<td>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 &gt;15%, or decrease in LVEF &gt;10% 29 additional pts who underwent AVR at the outset are not reported here</td>
<td>No pts died Progression to death, symptoms, increase in LVEDV or decrease in LVEF: 14.3%/y</td>
<td>Disease progression defined as symptoms, increase in LVEDV &gt;15%, or decrease in LVEF &gt;10% Disease progression associated with reduced myocardial systolic strain, systolic strain rate, and early diastolic strain rate</td>
</tr>
</tbody>
</table>

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; LVEDS, 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.
## Study Supplement 11. Vasodilator Therapy in Asymptomatic Patients With Chronic Aortic Regurgitation (Section 4.3.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>Primary Endpoint &amp; Results</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evangelista, 2005 (81)</td>
<td>Effects of vasodilator therapy on LV function and time to AVR</td>
<td>RCT/95</td>
<td>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</td>
<td>Asymptomatic, chronic, severe AR and normal LV function</td>
<td>LVEF &lt;50%, other valve disease. Hypertension, AF, CAD, aortic aneurysm</td>
<td>Open-label nifedipine (20 mg every 12 h) or open-label enalapril (20 mg/d)</td>
<td>No treatment</td>
<td>LVEF</td>
<td>Rate of AVR was similar among the groups: Control group 39% Enalapril group 50% Nifedipine group 41%; p=0.62</td>
</tr>
<tr>
<td>Scognomiglio, 1994 (76)</td>
<td>Assess whether vasodilator therapy reduces or delays the need for AVR</td>
<td>RCT/143</td>
<td>Intervention: Nifedipine (20 mg twice daily)-69 pts vs. Comparator: Digoxin (0.25 mg twice daily)-74 pts</td>
<td>Asymptomatic chronic severe AR with normal LV function</td>
<td>LVEF &lt;50%, recent or worsening AR, hypertension, CAD, AS, other valve disease.</td>
<td>Nifedipine</td>
<td>Digoxin</td>
<td>Time to AVR</td>
<td>AVR in 34%+6% of pts on digoxin versus 15%+3% of pts on nifedipine pts (p&lt;0.001) at 6 y follow-up</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Mean Follow-Up (y)</th>
<th>Inclusion Criteria, Outcome Assessed</th>
<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forman 1980 (85) 7377109</td>
<td>Determinants of survival after AVR</td>
<td>Retrospective, observational series; pts undergoing AVR 1972–1978; single institution</td>
<td>90</td>
<td>3</td>
<td>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</td>
<td>3-y survival: Overall 79±6% LVEF ≥50% 93±4% LVEF &lt;50% 64±10% p&lt;0.02 CI: ≥2.5 L/min/m² 93±4% CI: &lt;2.5 L/min/m² 63±10% p&lt;0.02</td>
<td>High-risk group identified by preoperative angiographic LVEF &lt;50% and/or CI: &lt;2.5 L/min/m²</td>
</tr>
<tr>
<td>Henry 1980 (86) 7353236</td>
<td>Determinants of survival after AVR</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1972–1977; single institution</td>
<td>50</td>
<td>3.7</td>
<td>Indications for AVR; symptoms Mean age 46 y (range 19–68 y) Preoperative angiography and hemodynamics Endpoint: survival</td>
<td>4-y survival: Overall 61% LVEF ≤55 mm 75% LVESD ≤55nm 38% p=0.006</td>
<td>High-risk group identified by preoperative echocardiographic LVFS &lt;25% and/or LVESD &gt;55 mm</td>
</tr>
<tr>
<td>Cunha 1980 (87) 7351849</td>
<td>Determinants of survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1973–1977; single institution</td>
<td>86</td>
<td>2.4 (range 1–5.4)</td>
<td>79 symptomatic pts, 7 asymptomatic Mean age 49.6 y (range 17–82 y) Preoperative echocardiographic (all pts) and hemodynamics (37 pts) Endpoint: survival</td>
<td>3-y survival: LVFS &gt;35% 100% LVFS 31-35% 91% LVFS ≤30% 78% p&lt;0.05 LVFS &gt;80% 100% LVFS &lt;60% 77% p&lt;0.05</td>
<td>High-risk group identified by preoperative echocardiographic LVFS &lt;30%. Mortality also significantly associated with preoperative LVESD. Among pts with FS &lt;30%, mortality higher in NYHA III-IV than in I-II.</td>
</tr>
<tr>
<td>Bonow 1980 (88) 5777072</td>
<td>Determinants of survival and LV function after AVR</td>
<td>Prospective, observational series; pts undergoing AVR 1972-1978; single institution</td>
<td>45</td>
<td>3.2</td>
<td>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</td>
<td>Among 32 pts with subnormal LVFS, those with good vs. poor exercise capacity had: Better survival (100% vs. 47%, p&lt;0.01). Lower postoperative LVESD (58±11 vs. 68±11 mm, p=0.005) Higher exercise LVEF (5±15 vs. 42±8%, p&lt;0.01)</td>
<td>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</td>
</tr>
<tr>
<td>Borow 1980 (89) 7377221</td>
<td>Determinants of LV function after AVR</td>
<td>Retrospective, observational series; pts undergoing AVR starting 1971; single institution</td>
<td>20</td>
<td>2.0 (range 0.5–5.0)</td>
<td>NYHA: II (20%), III (70%), IV (10%) Preoperative hemodynamics and angiography Postoperative echo Endpoint: LV function (LVFS)</td>
<td>Preoperative LVESVI correlated with postoperative LVFS (r=0.77) The 2 postoperative deaths occurred in pts with preoperative LVESVI &lt; 0.60 mL/m²</td>
<td>In symptomatic pts with AR, preoperative LVESVI is an important determinant of postoperative LV systolic function</td>
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<tr>
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</table>
| Greves 1981 (90) | Determinants of survival after AVR                                           | Retrospective, observational series | 42             | 3.7               | 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/m²  
Cardiac index: ≥2.5L/m²  
92±6%  
Cardiac index: ≥2.5L/m²  
86±16.1%  
\[p<0.02\]  
High-risk group identified by preoperative angiographic LVEF <45% and/or cardiac index <2.5 L/m²  
Among pts with LVEF <45%, mortality higher in NYHA III-IV than in I-II. |
| Kumpuris 1982 (91) | Determinants of survival, LV function, symptoms after AVR                   | Prospective, observational series   | 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):  
\text{Accuracy}  
LVEDD 72 mm 77%  
LVESD 50 mm 88%  
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)  | Determinants of LV function, symptoms after AVR                              | Prospective, observational series   | 32             | Range 1–6         | Group A: 25 pts with normal LVEDD after AVR (mean age 45 y, range 16–63 y) Group B: 7 pts with LVEDD >55 mm/m² 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 cm²/m² and R/Th ratio >3.6.  
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) | Determinants of LV function after AVR                                         | Retrospective, observational series | 47             | 3.4               | 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 35±6 vs. 24±6%  
—LVEDD 147±43 vs. 247±42 mL/m²  
—LVEF 54±7 vs. 42±9%  
Postoperative data, Group A vs. Group B:  
—LVEDD 53±8 vs. 63±7 mm  
Persistent LV dysfunction predicted by preoperative LVESD ≥75 mm and/or LVESD ≥55 mm.  
Note greater preoperative symptoms in Group B than Group A |

22
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Mean Follow-Up (y)</th>
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<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone 1984 (94) 6707364</td>
<td>Determinants of LV function after AVR</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1962–1977; single institution.</td>
<td>113</td>
<td>4.6±3.3</td>
<td>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)</td>
<td>43 pts died after AVR (8 from HF), no predictors of death Predictors of postoperative LVEDD ≤57 mm: LVESD, LVFS, R/T ratio Predictors of postoperative LVESD ≤40 mm: LVESD, LVEDD, LV mass</td>
<td>No preoperative variable predicted postoperative LV function. Normal LV size after AVR most likely in pts with preoperative LVFS &gt;26%, LVEDS &lt;55 mm, and LVEDD &lt;80 mm</td>
</tr>
<tr>
<td>Bonow 1985 (95) 4064269</td>
<td>Determinants of survival and LV function after AVR</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1976–1983; single institution.</td>
<td>80</td>
<td>3.75 (range 0.5–7.5)</td>
<td>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</td>
<td>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&lt;0.001) and LVESD (p&lt;0.01) 5 y survival: 96±3% in Group A, 63±12% in Group B (p&lt;0.001)</td>
<td>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 LVESD (both p&lt;0.001) than the others.</td>
</tr>
<tr>
<td>Daniel 1985 (96) 3156010</td>
<td>Determinants of survival, symptoms and LV function after AVR</td>
<td>Retrospective, observational series; pts undergoing AVR 1975–1983; single institution.</td>
<td>84</td>
<td>2.5</td>
<td>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</td>
<td>Survival at 2.5 y: 90.5% in pts with LVFS &gt;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 &gt;55 mm or LVFS ≤25%.</td>
<td>Outcome after AVR predicted by preoperative LVFS and LVEDS. Pts with preoperative LVFS ≤25% had greater postoperative LVEDS compared to those with LVFS &gt;25%. 62±10 vs. 54±7 mm (p&lt;0.05)</td>
</tr>
<tr>
<td>Cormier 1986 (97) 3727677</td>
<td>Determinants of survival after AVR</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1968–1983; single institution.</td>
<td>73</td>
<td>4.9±0.8 (range 0.3–14)</td>
<td>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/m²) Pts with CAD excluded Endpoint: Survival</td>
<td>84% survival at 8 y There were only 2 determinants of survival after AVR: LVF (p&lt;0.05) and LVESD (p&lt;0.05)</td>
<td>Overall survival good in asymptomatic/mildly symptomatic pts High-risk group identified by preoperative LVF &lt;40% and LVEDS ≤55 mm.</td>
</tr>
<tr>
<td>Sheiban 1986 (98) 3727678</td>
<td>Determinants of survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1973–1982; single institution.</td>
<td>84</td>
<td>6.5 (range 3–10)</td>
<td>NYHA: I (12%), II (33%), III (45%), IV (10%) Mean age 42 y (range 20–68) Echo, hemodynamics, and angiography Endpoint: Survival</td>
<td>10-y survival (p&lt;0.01): NYHA I 100%, II 86%, III 70%, IV 0% 5-y survival (p&lt;0.01): —92% in LVEDS ≤55 mm; —37% in LVEDS &lt;55 mm —81% in LVEF ≥50% ; 62% in LVEF &lt;50%</td>
<td>High-risk group identified by preoperative LVF &lt;50% and LVEDS &gt;55 mm. Severity of preoperative symptoms associated with late survival</td>
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</tbody>
</table>
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Study, Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Carabello 1986 (99) 3779916</td>
<td>Determinants of LV function after AVR in pts with preoperative LV dysfunction</td>
<td>Retrospective, observational series; pts undergoing AVR 1980–1987; single institution.</td>
<td>14</td>
<td>1.9±0.67 (range 0.5–6)</td>
<td>Pts with isolated severe AR and LVEF &lt;55% Mean age 49±6 y Pts with CAD excluded Preoperative hemodynamic and echo data; postoperative radionuclide angiography Endpoint: LV function</td>
<td>Preoperative LVESD 57±3 mm Correlation with postoperative LVEF: —LVEDD r=-0.47; p&lt;0.05 —LVEF r=0.55; p&lt;0.05 —R/Th r=0.56; p&lt;0.05 —LVESV r=-0.82; p&lt;0.05 —LVFS r=0.71; p&lt;0.01 —LVESD r=-0.91; p&lt;0.001</td>
<td>Postoperative LVEF correlated with preoperative LVESD, FS, LVEDD, R/Th ratio Postoperative LV EF most strongly associated with preoperative LVESD</td>
</tr>
<tr>
<td>Taniguchi 1987 (100) 3624657</td>
<td>Determinants of survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1978–1985; single institution.</td>
<td>62</td>
<td>3.8±2.2</td>
<td>Age 43±12 y (range 18–64) Group A: LVESV &lt;200 mL/m² (n=48), Group B: LVESV &gt;200 mL/m² (n=12) Pts with CAD excluded Preoperative hemodynamic and angiographic data Postoperative catheterization in 29 pts Endpoint: Survival and LV function</td>
<td>7-y survival 83±5% Preoperative LVESV index was most important indicator of postoperative death (p&lt;0.001) 6.5 y survival: 92±4% in Group A, 51±16% in Group B (p&lt;0.001) Postoperative data, Group A vs. Group B (p&lt;0.001) —LVEF: 62±7 vs. 42±8% —LVESV: 98±19 vs. 124±58 mL/m²</td>
<td>High-risk group identified by preoperative LVESV index &gt;200 mL/m² and/or LVEF &lt;40%. No cardiac deaths in Group A</td>
</tr>
<tr>
<td>Bonow 1988 (95) 4064269</td>
<td>Factors influencing short- and long-term changes in LV function after AVR</td>
<td>Prospective, observational series; pts undergoing AVR 1976–1983; single institution.</td>
<td>80</td>
<td>Range 3-7</td>
<td>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</td>
<td>Preoperative to early postoperative changes (p&lt;0.001): —LVEDD 75±6 to 56±9 mm —LVEF 43±9 to 51±16% —LVPS 247±50 to 163±42 dyne/cm² Early to late postoperative: no change in LVEDD or PSS, but further increase in LVEF to 56±19% (p&lt;0.001)</td>
<td>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</td>
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<tr>
<td>Michel 1995 (101) 5563993</td>
<td>Determinants of long-term survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1980–1994; single institution.</td>
<td>286</td>
<td>6</td>
<td>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 &lt;40% Group A: no postoperative LV dysfunction (n=247); Group B: postoperative LV dysfunction (n=28)</td>
<td>5- and 10-y survival 80% and 60%, respectively Preoperative data, Group A vs. Group B (p&lt;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%</td>
<td>Postoperative LV dysfunction predicted by severity of preoperative symptoms and preoperative LVEF, FS, LVESD, LVEDD. On multivariate analysis, preoperative symptoms (p&lt;0.01), LVESD (p&lt;0.03) and LVEF (p&lt;0.04) were significant factors. Determinants of survival not presented.</td>
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<tr>
<td>Klodas 1996 (102) 9806280</td>
<td>Impact of LV function on survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution</td>
<td>219</td>
<td>5-y and 10-y survival data reported</td>
<td>Group A: preoperative LVEDD &lt;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</td>
<td>Preoperative data, Group A vs. Group B (p&lt;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 y Preoperative 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. &lt;50% (p&lt;0.01): —10 y: 80±5% vs. 63±7%</td>
<td>Extreme LV dilatation associated with LV systolic dysfunction Preoperative LVEF, not degree of LV dilatation, associated with survival</td>
</tr>
<tr>
<td>Klodas 1997 (103) 9283535</td>
<td>Impact of symptom severity on survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution</td>
<td>289</td>
<td>5-y and 10-y survival data reported</td>
<td>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&lt;0.0001) Echo data in 249 pts Endpoint: survival</td>
<td>Preoperative data, Group A vs. Group B (p&lt;0.05): —LVEF: 5.3±11 vs. 4.9±14% 10-y survival, Group A vs. Group B (p&lt;0.001) —Total: 78±7% vs.45±4% —LVEF ≥50%: 82% vs. 40% —LVEF &lt;50%: 73% vs. 40% —Men: 80% vs. 55% —Women: 73% vs. 21% —CAD: 76% vs. 39% —No CAD: 79% vs. 48%</td>
<td>High-risk group identified by symptom severity and preoperative LVEF &lt;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</td>
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<tr>
<td>Turina 1998 (104) 9852889</td>
<td>Determinants of survival after AVR</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1970–1983; single institution</td>
<td>192</td>
<td>18.7 (range 13–26)</td>
<td>Mean age 44 y Endpoint: Survival</td>
<td>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.</td>
<td>High-risk group identified by symptom severity, low LVEF, and elevated ESV.</td>
</tr>
<tr>
<td>Chaliki 2002 (105) 12438264</td>
<td>Survival after AVR in pts with normal versus reduced LV function</td>
<td>Retrospective, observational series; consecutive pts undergoing AVR 1980–1995; single institution</td>
<td>450</td>
<td>8.1 (median)</td>
<td>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 &lt;35% LVEF measured by left ventriculography</td>
<td>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&lt;0.001) 10-y HF rate, Group A vs. B vs. C: 9%, 17%, 25% (p&lt;0.003) Postoperative change in LVEF, Group A vs.</td>
<td>Pts with markedly low LVEF incur 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</td>
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</tbody>
</table>
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
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</tr>
</thead>
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<td>Tornos 2006 (106) 16516086</td>
<td>Determinants of survival after AVR</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1982–2002; single institution</td>
<td>170 10±6 (range 1–22)</td>
<td>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 &lt;45% or LVESD &gt;55 mm) Echo data</td>
<td>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</td>
<td>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.</td>
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<tr>
<td>Bhudia 2007 (107) 17397676</td>
<td>Survival after AVR in pts with marked LV dysfunction compared to normal LV function or mild LV dysfunction</td>
<td>Prospective, observational series; consecutive pts undergoing AVR 1972–1999; single institution</td>
<td>724 8.3±6.5</td>
<td>Group A (88 pts, age 56±12) with severe LV dysfunction (LVEF &lt;30%) Group B (636 pts, age 50±15) with either less severe LV dysfunction or normal LV function</td>
<td>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</td>
<td>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</td>
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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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean Follow-Up</th>
<th>Procedure</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Average Morphology Score*</th>
<th>Mitral Gradient (mm Hg) Pre</th>
<th>Mitral Valve Area (cm²) Pre</th>
<th>Mitral Valve Area (cm²) Post</th>
<th>Restenosis (%)</th>
<th>Freedom From Reintervention (%)</th>
<th>NYHA I (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel 1991 (108) 1918709</td>
<td>Immediate</td>
<td>PMBC</td>
<td>23</td>
<td>30±11</td>
<td>6.0</td>
<td>12±4</td>
<td>4±3</td>
<td>0.8±0.3</td>
<td>2.1±±0.7†</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patel 1991 (109) 2013139</td>
<td>7 mo</td>
<td>CC</td>
<td>22</td>
<td>26±26</td>
<td>6.0</td>
<td>12±5</td>
<td>6±3</td>
<td>0.7±0.2</td>
<td>1.5±0.3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Turk 1993 (110) 8465732</td>
<td>22 mo</td>
<td>PMBC</td>
<td>20</td>
<td>27±8</td>
<td>7.2</td>
<td>18±4</td>
<td>10±2</td>
<td>0.8±0.2</td>
<td>1.5±0.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Arora 1993 (111) 8094354</td>
<td>3 y</td>
<td>CC</td>
<td>100</td>
<td>19±5</td>
<td>N/A</td>
<td>20±6</td>
<td>12±2</td>
<td>0.8±0.4</td>
<td>1.7±0.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Reyes 1994 (111) 8084354</td>
<td>3 y</td>
<td>PMBC</td>
<td>30</td>
<td>30±9</td>
<td>N/A</td>
<td>6.7</td>
<td>N/A</td>
<td>0.9±0.3</td>
<td>2.4±0.4†</td>
<td>10</td>
<td>N/A</td>
</tr>
<tr>
<td>Ben Farhat 1998 (112) 9482525</td>
<td>7 y</td>
<td>OC</td>
<td>30</td>
<td>29±12</td>
<td>N/A</td>
<td>6.0</td>
<td>N/A</td>
<td>0.9±0.2</td>
<td>1.5±0.4</td>
<td>N/A</td>
<td>90</td>
</tr>
<tr>
<td>Colombo 1999 (113) 10386411</td>
<td>38 mo</td>
<td>PMBC</td>
<td>111</td>
<td>47±14</td>
<td>N/A</td>
<td>6.0</td>
<td>N/A</td>
<td>0.9±0.2</td>
<td>1.5±0.3</td>
<td>N/A</td>
<td>93</td>
</tr>
<tr>
<td>Cotrufo 1999 (113) 10386411</td>
<td>50 mo</td>
<td>OC</td>
<td>52</td>
<td>49±10</td>
<td>6.2</td>
<td>N/A</td>
<td>1.0±0.2</td>
<td>2.3±0.3</td>
<td>18</td>
<td>96</td>
<td>84</td>
</tr>
</tbody>
</table>

*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).
### Data Supplement 14. Echocardiographic Prediction of Outcome of Percutaneous Balloon Mitral Commissurotomy (Section 6.2.3)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean Follow-Up, mo</th>
<th>Echo Criteria</th>
<th>Number of Patients</th>
<th>Age (y±SD)</th>
<th>Survival (%)</th>
<th>Survival Free of Events (%)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al., 1992</td>
<td>36±20</td>
<td>Score ≤8 Score &gt;8</td>
<td>84 52</td>
<td>N/A</td>
<td>N/A</td>
<td>68% at 5 y 28% at 5 y</td>
<td>Death, MVR, repeat PMBC</td>
</tr>
<tr>
<td>Palacios et al., 1995</td>
<td>20±12</td>
<td>Score ≤8 Score &gt;8</td>
<td>211 116</td>
<td>48±14 64±11</td>
<td>98% at 4 y 39% at 4 y</td>
<td>98% at 4 y 39% at 4 y</td>
<td>Death, MVR, NYHA III-IV symptoms</td>
</tr>
<tr>
<td>Dean et al., 1996</td>
<td>38±16</td>
<td>Score ≤8 Score 8–12 Score &gt;12</td>
<td>272 306 24</td>
<td>49±13 56±15 58±15</td>
<td>95% at 4 y 83% at 4 y 24% at 4 y</td>
<td>N/A</td>
<td>Death</td>
</tr>
<tr>
<td>Jung et al., 1996</td>
<td>32±18</td>
<td>Group 1 Group 2 Group 3</td>
<td>87 311 130</td>
<td>46±13</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cannan et al., 1997</td>
<td>22±10</td>
<td>Com Ca-Com Ca+</td>
<td>120 29</td>
<td>N/A</td>
<td>N/A</td>
<td>86% at 3 y 40% at 3 y</td>
<td>Death, MVR, repeat PMBC</td>
</tr>
<tr>
<td>Palacios et al., 2002</td>
<td>50±44</td>
<td>Score &gt;8 Score ≤8</td>
<td>278 601</td>
<td>63±14 51±14</td>
<td>82% at 12 y 57% at 12 y</td>
<td>38% at 12 y 22% at 12 y</td>
<td>Death, MVR, repeat PMBC</td>
</tr>
</tbody>
</table>

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 (Jung, 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.
## 2014 Valvular Heart Disease Guideline Data Supplements

### Data Supplement 15. Randomized Trials of Percutaneous Mitral Balloon Commissurotomy Versus Surgery for Mitral Stenosis (Section 6.2.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel 1991 (108) 1918709</td>
<td>Compare PMBC by single catheter technique versus CC</td>
<td>RCT/45</td>
<td>Intervention: 23 PMBC vs. comparator: 22 CC</td>
<td>Symptomatic NYHA II or III, light MS</td>
<td>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</td>
<td>PBMC</td>
<td>Closed surgical valvotomy</td>
</tr>
<tr>
<td>Ben 1998 (112) 9462525</td>
<td>Compare the early invasive and long-term (7 y) clinical and echo follow-up results of PMBC with those of OC and CC for the treatment of tight pliable rheumatic MS</td>
<td>RCT/90</td>
<td>Intervention: PMBC vs. comparator: CC; OC</td>
<td>Rheumatic light to moderate mitral valve stenosis (MVA &lt;1.3 cm²), Other valve disease, previous thromboembolism, mitral valve calcification, and left atrium thrombus, AF, severe pulmonary hypertension or mild-to-moderate TR</td>
<td>PBMC</td>
<td>CC or OC</td>
<td>Increase in Gorlin MVA: PMBC (from 0.8±0.16 to 2.2±0.4 cm²), OC (from 0.9±0.2 to 2.2±0.4 cm²), CC (from 0.9±0.2 to 1.6±0.4 cm²). Residual MS (MVA &lt;1.5 cm²): 0% after PMBC 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 PMBC and OC (1.8±0.4 cm²) than after CC (1.3±0.3 cm²; p&lt;0.001). Restenosis (MVA &lt;1.5 cm²) rate was 6.6% after PMBC or OC vs. 37% after CC. Residual ASD in 2 pts and 3+ MR in 1 pt in the PMBC group. NYHA class I in 87% of pts after PMBC and 90% of pts after OC vs. CC 33% (p&lt;0.0001). Freedom from reintervention 90% after PMBC, 93% after OC, and 50% after CC.</td>
</tr>
<tr>
<td>Turi 1991 (109) 2013139</td>
<td>Compare PMBC with surgical CC</td>
<td>RCT/40</td>
<td>Intervention: 20 PMBC vs. Comparator: 20 CC</td>
<td>Pts deemed acceptable as candidates for both procedures</td>
<td>N/A</td>
<td>PBMC</td>
<td>Surgical CC</td>
</tr>
</tbody>
</table>
| Arora 1993 (110) 8465732 | Compare the immediate and long-term results of PMBC vs. CMC | RCT/200 | Intervention: 100 PMBC 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 cm²; CC: 0.79±0.21 to 2.2±0.85 cm²; p=NS). MR developed in 14 pts after PMBC and in 12 pts after CC. Restenosis (defined as a loss of >50% of the achieved
<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reyes 1994 (111) 8084354</td>
<td>Compare PBMC to OC for treatment of rheumatic MS</td>
<td>RCT/60</td>
<td>Intervention: 30 vs. Comparator: 30</td>
<td>Severe rheumatic MS, in sinus rhythm, no severe subvalvular disease/ calcification or more than mild MR</td>
<td>Coexisting other cardiac or valve disease, stroke, severe pulmonary hypertension, low body weight, Lutembacher's syndrome, and pt decision not to be randomized</td>
<td>PBMC</td>
<td>Open surgical commissurotomy</td>
</tr>
<tr>
<td>Cotrufo 1999 (113) 10386411</td>
<td>Compare PPMC vs. OC</td>
<td>RCT/193</td>
<td>Intervention: PBMC 111 vs. Comparator: OC 82</td>
<td>N/A</td>
<td>N/A</td>
<td>PBMC</td>
<td>OC</td>
</tr>
</tbody>
</table>

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.
# 2014 Valvular Heart Disease Guideline Data Supplements

## Data Supplement 16. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation (Section 7.3.3)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Design</th>
<th>Type of Surgery</th>
<th>Number of Patients</th>
<th>Outcome Assessed</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuler 1979 (122) 436214</td>
<td>Retrospective</td>
<td>MVR</td>
<td>20</td>
<td>LV function</td>
<td>12 pts with average LVEF 0.70 had normal postoperative LVEF; 4 pts with average LVEF 0.58 had postoperative LVEF 0.25.</td>
</tr>
<tr>
<td>Phillips 1981 (123) 7282546</td>
<td>Retrospective</td>
<td>MVR</td>
<td>105</td>
<td>Survival</td>
<td>LVEF &lt;0.50 predicted poor survival.</td>
</tr>
<tr>
<td>Zile 1984 (124) 6693815</td>
<td>Prospective</td>
<td>MVR</td>
<td>16</td>
<td>HF, LV function</td>
<td>LVEF index &gt;2.6 cm/m² (45 mm) and LVFS &lt;0.32 predicted poor outcome.</td>
</tr>
<tr>
<td>Crawford 1990 (125) 2317900</td>
<td>Prospective</td>
<td>MVR</td>
<td>48</td>
<td>Survival, LV function</td>
<td>LVEF &lt;0.50 predicted reduced survival; ESV &gt;50 mL/m² predicted persistent LV dilatation.</td>
</tr>
<tr>
<td>Wisenbaugh 1994 (126) 8012639</td>
<td>Registry</td>
<td>MVR</td>
<td>26</td>
<td>Survival, LV function</td>
<td>LVEF, LVESD, and FS predicted poor survival and LV function; only LVESD significant in multivariate analysis.</td>
</tr>
<tr>
<td>Enriquez-Sarano 1994 (127) 8044955</td>
<td>Retrospective</td>
<td>MVR</td>
<td>214</td>
<td>Survival</td>
<td>LVEF &lt;0.60 predicted poor survival whether MVR or CP was preformed; LVEF estimated by echo FS or visual analysis.</td>
</tr>
<tr>
<td>Enriquez-Sarano 1994 (128) 7930287</td>
<td>Retrospective</td>
<td>MVR</td>
<td>195</td>
<td>Survival</td>
<td>LVEF, LVESD, LV diameter/thickness ratio and end-systolic wall stress predicted outcome; LVEF estimated by echo FS or visual analysis.</td>
</tr>
</tbody>
</table>

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.
### Data Supplement 17. Primary Mitral Regurgitation—Evidence for Intervention (Section 7.3.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribouilloy 1999 (129)</td>
<td>Assess impact of symptom status on outcome</td>
<td>Retrospective</td>
<td>478</td>
<td>Mitral surgery</td>
<td>NYHA class I, II, III, IV</td>
<td>Advanced preoperative symptoms increased operative mortality by 10 fold. Long-term survival also reduced.</td>
</tr>
<tr>
<td>Gillinov 2010 (130)</td>
<td>Assess impact of symptoms on outcomes</td>
<td>Retrospective propensity-matched</td>
<td>4,253</td>
<td>MVR</td>
<td>NYHA all class</td>
<td>Even NYHA class II preoperative symptoms impaired late survival.</td>
</tr>
<tr>
<td>Rosenhek 2006 (131)</td>
<td>Assess outcome with watchful waiting</td>
<td>Prospective</td>
<td>132</td>
<td>Watchful waiting for severe MR</td>
<td>N/A</td>
<td>Survival for watchful waiting identical to age normal population, but triggers for surgery occurred early after enrollment in 50%.</td>
</tr>
<tr>
<td>Kang 2009 (132)</td>
<td>Assess outcome with watchful waiting</td>
<td>Prospective</td>
<td>447</td>
<td>Mitral surgery</td>
<td>Early surgery vs. watchful waiting</td>
<td>Early surgery appeared superior, but several unoperated pts refused surgery despite presence of triggers.</td>
</tr>
<tr>
<td>Enriquez-Sarano 1994 (127)</td>
<td>Assess predictors of outcome</td>
<td>Retrospective</td>
<td>409</td>
<td>Mitral surgery</td>
<td>LVEF &gt;60, 50-60, &lt;50</td>
<td>Survival at 10 y, 72% for LVEF &gt;60, 53%, 50-60, 32%, &lt;50.</td>
</tr>
<tr>
<td>Tribouilloy 2009 (133)</td>
<td>Assess impact of LVESD on outcomes</td>
<td>Retrospective</td>
<td>739</td>
<td>Mitral surgery</td>
<td>LVESD &lt;40 vs. ≥40</td>
<td>LVESD &gt;40 mm nearly doubled late mortality risk.</td>
</tr>
<tr>
<td>Enriquez-Sarano 2005 (134)</td>
<td>Assess impact of MR severity</td>
<td>Prospective</td>
<td>450</td>
<td>Mitral surgery</td>
<td>ERO of different sizes</td>
<td>ERO &gt;0.4 cm² nearly tripled mortality, but mortality was reduced by surgery.</td>
</tr>
<tr>
<td>Ghoreshi 2011 (135)</td>
<td>Assess impact of pulmonary HTN on outcome</td>
<td>Retrospective</td>
<td>873</td>
<td>Mitral surgery</td>
<td>Preoperative-pulmonary HTN of various degrees</td>
<td>5 y survival 88% for PAP &lt;40 vs. 52%, PAP &gt;60.</td>
</tr>
<tr>
<td>Goldman 1987 (136)</td>
<td>Compare LV function after replace vs. repair</td>
<td>Prospective</td>
<td>18</td>
<td>Mitral surgery</td>
<td>Repair vs. replacement</td>
<td>LVEF fell following replacement, but not repair.</td>
</tr>
<tr>
<td>David 1984 (137)</td>
<td>Compare outcome with and without chordal preservation</td>
<td>Prospective</td>
<td>27</td>
<td>Mitral surgery</td>
<td>MV surgery with and without chordal preservation</td>
<td>LVEF decreased without preservation, but was maintained with preservation.</td>
</tr>
<tr>
<td>Rozich 1992 (138)</td>
<td>Examined LVEF</td>
<td>Retrospective</td>
<td>15</td>
<td>Mitral surgery</td>
<td>Chordal preservation vs. destruction</td>
<td>Afterload increased following chordal destruction, but decreases following preservation.</td>
</tr>
<tr>
<td>Grigioni 2008 (139)</td>
<td>Outcome of repair vs. replacement</td>
<td>Prospective</td>
<td>394</td>
<td>Mitral surgery</td>
<td>Repair vs. replacement vs. nonsurgery</td>
<td>92% 54 y survival for repair 80% for replacement.</td>
</tr>
<tr>
<td>Study Name, Author, Year</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Size (N)</td>
<td>Study Intervention Group (n)</td>
<td>Study Comparator Group (n)</td>
<td>Outcome</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Gillinov 2008 (140) 18721551</td>
<td>Outcome of repair vs. replacement</td>
<td>Retrospective</td>
<td>328</td>
<td>N/A</td>
<td>Repair vs. replacement propensity</td>
<td>5, 10, 15 y survival 95, 87, 68 repair vs. -80, 60, 44 replacement.</td>
</tr>
</tbody>
</table>

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.
### 2014 Valvular Heart Disease Guideline Data Supplements

#### Data Supplement 18. Secondary Mitral Regurgitation—Evidence for Intervention (7.4.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang 2006 (141)</td>
<td>Outcome surgery in moderate-to-severe ischemic MR</td>
<td>Retrospective</td>
<td>107</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>Higher operative mortality with CABG and MV repair vs CABG alone (12% vs 2%) but similar 5 year survival (88% vs 87%)</td>
</tr>
<tr>
<td>Rossi 2011 (142)</td>
<td>Impact of SMR on outcome</td>
<td>Retrospective</td>
<td>1,256</td>
<td>None</td>
<td>Impact of SMR on HF</td>
<td>After adjusting for LVEF and other factors-SMR increased mortality by 2-fold</td>
</tr>
<tr>
<td>Wu 2005 (143)</td>
<td>Impact of surgery on moderate-severe MR</td>
<td>Retrospective</td>
<td>126</td>
<td>Surgery with mitral annuloplasty</td>
<td>Med Rx</td>
<td>No survival advantage to mitral valve annuloplasty</td>
</tr>
<tr>
<td>Mihaljevic 2007 (144)</td>
<td>Impact of mitral surgery moderate-severe on SMR</td>
<td>Retrospective</td>
<td>290</td>
<td>CABG + MV surgery</td>
<td>CABG</td>
<td>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</td>
</tr>
<tr>
<td>Benedetto 2009 (145)</td>
<td>Impact of MV surgery on SMR</td>
<td>Meta-analysis</td>
<td>2,479</td>
<td>CAGB+MV surgery</td>
<td>CABG</td>
<td>No difference in survival or symptomatic status</td>
</tr>
<tr>
<td>Fattouch 2009 (146)</td>
<td>Impact of MV surgery in ischemic MR</td>
<td>Randomized prospective</td>
<td>102</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>No difference in mortality. Repair group had reduced cardiac dimensions and symptoms vs. CABG alone</td>
</tr>
<tr>
<td>Deja 2012 (147)</td>
<td>Impact of repair in ischemic SMR</td>
<td>Randomized to medical Rx vs. surgery</td>
<td>104</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>53% mortality CABG, vs. 43% mortality CABG + MVR (p=NS); after adjustment CABG + MVR had better survival</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size, Details</th>
<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreyfus, 2005 (148)</td>
<td>Determine benefit of TV annuloplasty based on intraoperative measurement of TA size</td>
<td>Prospective, observational series 1989–2001; single surgeon</td>
<td>311 pts undergoing MVR for chronic severe MR. 163 pts with TA &lt;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 &gt;2+ TR; 2 pts in Group 2 had ≥3+ TR.</td>
<td>Postoperative TR grade 2.1±1.0 Group 1 vs. 0.4±0.6 Group 2; (p&lt;0.001). TR severity increased &gt;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.</td>
<td>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.</td>
</tr>
<tr>
<td>Chan, 2009 (149)</td>
<td>Determine the effects of TR and TV repair on clinical and TTE outcomes in pts undergoing MV replacement.</td>
<td>Retrospective, observational, single center, 1990–2005</td>
<td>624 pts undergoing MV replacement. 231 with ≥2+TR; 125 received TVR, 106 did not. Mean follow-up 6.8±4.8 y.</td>
<td>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.</td>
<td>Study spans 15 y. Multiple annuloplasty techniques used. 22% of pts had suture annuloplasty.</td>
</tr>
<tr>
<td>Calafiore, 2009 (150)</td>
<td>Evaluate clinical outcomes of pts undergoing TV annuloplasty for ≥moderate TR at time of MVR for functional MR.</td>
<td>Retrospective, observational, single center, 1988–2003</td>
<td>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.</td>
<td>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&lt;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.</td>
<td>Study span 15 y. De Vega annuloplasty in all pts. All pts had functional MR. Incomplete TTE follow-up.</td>
</tr>
<tr>
<td>Di Mauro, 2009 (4) (151)</td>
<td>Evaluate impact of ≥moderate TR on midterm outcomes of pts undergoing surgery for functional MR</td>
<td>Retrospective, observational, single center 1988–2003</td>
<td>165 pts with functional MR and untreated TR 102 pts with 0–1+TR 63 pts with 2–3+TR</td>
<td>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&lt;0.001). TR grade declined after MV surgery, but then progressed in pts with 2–3+ preoperative TR.</td>
<td>Study span 15 y. Incomplete TTE follow-up. No information on success of MV surgery. Same pt cohort as reported by Calafiore 2009.</td>
</tr>
</tbody>
</table>
| Yilmaz, 2011 (153) | 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
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size, Details</th>
<th>Outcomes</th>
<th>Comments, Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calafiore, 2011</td>
<td>Determine benefit of TV annuloplasty for TR based on TA diameter</td>
<td>Retrospective, observational, single center 2006–2008</td>
<td>298 pts with ≥1+ TR undergoing MV surgery. 167 underwent TVR, 108 with ≥moderate TR and 59 with TA &gt;24 mm. 137 did not have TVR, 16 with ≥moderate TR and 81 with TA &gt;24 mm.</td>
<td>In pts who did not undergo TVR, TA &gt;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).</td>
<td>DeVega annuloplasty used in all pts with TA &lt;28 mm. Small cohort sizes.</td>
</tr>
<tr>
<td>Navia, 2012</td>
<td>Identify factors associated with TVR; assess safety and efficacy of TVR</td>
<td>Retrospective, observational, single center series 1997–2008</td>
<td>91(5%) of 1,724 pts with 2+ TR undergoing left-sided heart valve surgery. Propensity analysis performed for 91 matched pairs.</td>
<td>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 (&lt;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.</td>
<td>Multiple TVR techniques used Limited long-term outcome and TTE data. Matched pairs differed significantly.</td>
</tr>
<tr>
<td>Kim, 2012</td>
<td>Assess clinical and TTE outcomes of TVR in pts with mild-to-moderate TR at time of MV replacement</td>
<td>Retrospective, observational, single center, 1997-2008</td>
<td>236 pts with mild-moderate TR undergoing mechanical MV replacement for rheumatic disease. 123 pts underwent TVR. 113 pts did not undergo TVR.</td>
<td>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).</td>
<td>All pts had rheumatic MV disease. Groups significantly unbalanced at baseline. Limited TTE follow-up information, especially regarding MV prosthesis function, PA pressures, etc.</td>
</tr>
<tr>
<td>Benedetto 2012</td>
<td>Determine if TV annuloplasty in pts with TA dilatation and ≤moderate TR prevents TR progression after MV surgery</td>
<td>Randomized, prospective, single institution, 2008-2009</td>
<td>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.</td>
<td>≥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).</td>
<td>Small sample size. Nonblinded endpoint assessment.</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Size</th>
<th>Methods</th>
<th>Patient Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammermeister 2000 (158) 11028464</td>
<td>575 pts undergoing isolated AVR (394) or MVR (181) at 13 VA medical centers (1977–1982)</td>
<td>RCT</td>
<td>Isolated AVR or MVR. Concurrent CABG performed in 39% of AVR and 96% of MVR pts.</td>
<td>15 y</td>
<td>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±6% vs. 5±4%; p=0.0002). Primary valve failure nearly always (93%) occurred in pts &lt;65 y. AVR reoperation was higher after BHV vs. MHV (29±5% vs. 10±3%; p=0.004). No statistically significant difference for MVR.</td>
<td>Pts receiving mechanical MVR were older and had more hypertension than those with a bioprosthetic MVR.</td>
</tr>
<tr>
<td>Oxenham, 2003 (159) 12807838</td>
<td>541 pts undergoing MVR (261), AVR (211), or both (61) 1975–1979</td>
<td>RCT</td>
<td>Mean age 53.9 (10.6) y. 56% female. Additional valve procedures or not eligible for VKA anticoagulation.</td>
<td>20 y</td>
<td>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.</td>
<td>Older generation valve types.</td>
</tr>
<tr>
<td>Stassano 2009 (160) 19892237</td>
<td>310 pts undergoing AVR (201), MVR (109), or both (61) 1975–1979</td>
<td>RCT</td>
<td>Age 55–70 y Other valve surgery. Contraindication to VKA anticoagulation.</td>
<td>Mean 106±28 mo</td>
<td>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.</td>
<td>Power may not be adequate to detect a clinically meaningful difference at longer follow-up.</td>
</tr>
<tr>
<td>Khan 2001 (161) 11479498</td>
<td>Initial AVR in 1389 pts, MVR in 915 pts, 1976–2001 at</td>
<td>Retrospective, observational</td>
<td>Age 64.5±12.9 y for MHV Age 72.0±12.6 y for BHV Homografts, combined MHV and BHV procedure, any previous</td>
<td>20 y</td>
<td>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.</td>
<td>Not prospective, not randomized. Concurrent CABG in</td>
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### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Size</th>
<th>Methods</th>
<th>Patient Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan 2006 (162)</td>
<td>3,063 pts undergoing AVR 1982–1998</td>
<td>Retrospective, observational</td>
<td>2,195 BHV and 980 MHV.</td>
<td>Previous cardiac surgery</td>
<td>Valve-related mortality (per pt-y): BHV 1.0% vs. MHV 0.7%</td>
<td>Not randomized. AVR only. Concomitant CABG in 43.5% of BHV pts and 26.0% of MHV pts.</td>
</tr>
<tr>
<td>Kulik 2006 (163)</td>
<td>659 pts age 50–65 y with initial AVR or MVR</td>
<td>Prospective, observational</td>
<td>AVR in 388 (MHV 306, BHV 48). MVR in 236 (MHV 188, BHV 48).</td>
<td>Enrolled only if survived perioperative period. Valve repair excluded.</td>
<td>Freedom from primary endpoint MAPE at 10 y (reoperation, endocarditis, major bleeding, or thromboembolism): AVR MHV 70±4.1% vs. BHV 41.0±3.1%; 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</td>
<td>Not randomized. Surgeon choice of valve type. Concurrent CABG in 29%.</td>
</tr>
<tr>
<td>Ruel 2007 (164)</td>
<td>567 pts undergoing AVR or MVR</td>
<td>Retrospective, observational</td>
<td>Age &lt;60 y. First heart valve operation.</td>
<td>N/A</td>
<td>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: 0.95; 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%.</td>
<td>Not randomized or prospective, follow-up available in only 23% of original cohort.</td>
</tr>
<tr>
<td>van Geldorp 2009 (165)</td>
<td>Bioprosthetic AVR=2,860 (73%) vs. mechanical AVR=1,074 (27%)</td>
<td>Retrospective cohort (1982–2003) Microsimulation used to calculate age-specific pt 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.</td>
<td>Bioprosthetic AVR: mean age=70 y, mean follow-up=6.1 y. Mechanical AVR: mean age=58 y, mean follow-up=6.5 y, CABG=28%</td>
<td>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.</td>
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</tbody>
</table>
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Size</th>
<th>Methods</th>
<th>Patient Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badhwar 2012 (166) 22364968</td>
<td>172 pts undergoing isolated AVR or MVR (2003–2007)</td>
<td>Prospective, nonrandomized, matched pairs for BP vs. MP</td>
<td>Mean age $56.2\pm9.6$ y (range, 24–72 y).</td>
<td>Limited 5 y survival based on comorbidity</td>
<td>Median follow-up 4.0 y</td>
<td>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</td>
</tr>
<tr>
<td>Weber 2012 (167) 22341653</td>
<td>206 pts undergoing AVR (2000–2009)</td>
<td>Retrospective, with propensity matching of 103 BP to 103 MP AVR</td>
<td>Age &lt;60 y. AVR with or without concurrent CABG, aortic root surgery, mitral or tricuspid valve repair.</td>
<td>Additional valve replacement.</td>
<td>Median follow-up 33±24 mo (2–120 mo)</td>
<td>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</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Study Size and Comparator (N)</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersingl 2007 (168) 17578050</td>
<td>Prospective, observational</td>
<td>Pts with MHV undergoing major surgery (n=25) or minor surgery (n=58), pacemaker implantation (n=21), or cardiac cath (n=34)</td>
<td>N/A</td>
<td>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.</td>
<td>Not randomized, no comparison group, relatively small study group.</td>
</tr>
<tr>
<td>Spyropoulos 2008 (169) 18805116</td>
<td>Observational, prospective, multicenter registry in USA, Canada</td>
<td>Adults undergoing elective surgery or invasive procedure with a mechanical valve on long-term VKA</td>
<td>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)</td>
<td>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 &lt;24 hours (68.6% vs. 6.8%; p &lt;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.</td>
<td>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)</td>
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<tr>
<td>Pengo 2009 (170) 19470892</td>
<td>Prospective inception cohort at 22 Italian centers, 2005–2007</td>
<td>Adults undergoing surgical or invasive procedures that required interruption of long-term VKA therapy</td>
<td>Body weight &lt;40 kg. Creatinine &gt;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.</td>
<td>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.</td>
<td>Only 15% had mechanical valves, no comparison group. Safety in pts with MHV valves has not been conclusively established</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Type</td>
<td>Patient Population</td>
<td>Study Size and Comparator (N)</td>
<td>Outcomes</td>
<td>Study Limitations</td>
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<td>Events at 3 mo N (%)</td>
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<td></td>
<td>No Heparin</td>
<td>LMWH Only</td>
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<td></td>
<td>N=213</td>
<td>N=243</td>
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<tr>
<td>Daniels 2009 (171) 19232682</td>
<td>Retrospective cohort, 1997–2003</td>
<td>MHV on chronic VKA therapy undergoing invasive procedures or surgery</td>
<td>N/A</td>
<td>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.</td>
<td>Events at 3 mo N (%): Thromboembolism (1.0, 0.0, 2.3), Major Bleeding (5.2, 9.3, 6.6), Minor Bleeding (13.6, 13.5, 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.</td>
</tr>
<tr>
<td>Bui HT 2009 (172) 19892063</td>
<td>Retrospective cohort study</td>
<td>173 pts on VKA anticoagulation for MHV (n=90) or for nonvalvular AF undergoing invasive or surgical procedures</td>
<td>Age &lt;18 y, Pregnancy, Hypercoagulable condition, bioprosthetic valve</td>
<td>130 bridging episodes with LMWH were used to compare outcomes in MHV vs. pts with AF.</td>
<td>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).</td>
</tr>
<tr>
<td>Bilecker 2012 (173) 22591673</td>
<td>Prospective cohort, single center</td>
<td>Consecutive pts undergoing noncardiac surgery</td>
<td>Bioprosthetic valves, severe liver or renal disease, contraindication to heparin</td>
<td>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.</td>
<td>Events (3 mo) N (%): Bleeding (19.8, 14.2, NS), Thromboembolism (3.6, 2%, NS), Mortality (1.4, 1.3, NS), Cardiovascular events (10.8, 10.7, NS).</td>
</tr>
<tr>
<td>Weiss 2013 (174) 236449452</td>
<td>Retrospective, single-center cohort study</td>
<td>Consecutive pts requiring postoperative bridging therapy after cardiac surgery during a 19 mo period</td>
<td>N/A</td>
<td>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.</td>
<td>Events (by hospital discharge) N (%): Full dose LMWH (N=210, 0.5%, 5.5%, 0.003), Low dose LMWH (N=210, 0.5%, 5.5%, 0.277), Thromboembolism (5%, 9%, 0.126), Bleeding (11%, 5%, 0.003), Hospital stay (d) (15.1±9.3, 12.5±8.1).</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AVR, aortic valve replacement; DVR, double-valve replacement; FD, full 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.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Intervention vs. Comparator (n)</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviri 1991 (175) 1993782</td>
<td>Observational, single center, surgical treatment for PVT, 1980–1989</td>
<td>n=100 (32 male) aged 5 mo–82 y (median 32 y) with PVT (n=61) or pannus (n=7), or both (n=44)</td>
<td>Only included pts undergoing surgery for PVT or pannus. AVR in 51 (48%), MVR in 49 (46%), and both in 6 (6%)</td>
<td>Early mortality 12.3% (n=13) Perioperative mortality higher in pts with NYHA IV (17.5%) vs. NYHA I-III (4.7%) symptoms, p&lt;0.05</td>
<td>Older generation mechanical PHV, chart-recovered data, various diagnostic approaches.</td>
</tr>
<tr>
<td>Tong 2004 (176) 14715187</td>
<td>International registry of pts with suspected PVT, 1985–2001</td>
<td>107 pts (71 females; age 24 to 86 y) from 14 centers (6 in the U.S.) MVR=79, AVR=13, TVR=15</td>
<td>Only included pts with suspected PVT who underwent TEE and were treated with FT</td>
<td>Hemodynamic success rate 85% Overall complications rate 17.8% Death in 5.6% Independent predictors of complications: 1) thrombus area &gt;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</td>
<td>Not all pts had PHV obstruction, thrombolysis criteria not standardized. Goal of study was to assess role of TEE measurement of thrombus burden.</td>
</tr>
<tr>
<td>Rouaidut 2009 (177) 19427604</td>
<td>Observational, nonrandomized single center over 20 y, 1978–2001</td>
<td>n=263 episodes in 210 pts (98% left sided valves)</td>
<td>Decision for surgical vs. FT made by each clinician. Surgery=136 Fibrinolysis=127</td>
<td>Surgery vs. FT</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
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<td>Restored valve fx 89% 70.9% &lt;0.001</td>
<td>Mortality (6 y) 26% 48% 0.002</td>
</tr>
<tr>
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<td>Thromboembolism 0.7% 15% &lt;0.001</td>
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<td>Major Comp. 11.1% 25.2% 0.05</td>
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<tr>
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<td></td>
<td></td>
<td>Recurrent PVT 11% 25% 0.021</td>
<td></td>
</tr>
<tr>
<td>Karthikeyan 2009 (178) 19738134</td>
<td>Randomized, controlled, single Indian center</td>
<td>120 pts with first episode of left sided PVT</td>
<td>Contraindications to FT, symptom duration &gt;2 wk, recurrent PVT</td>
<td>Accelerated infusion of streptokinase vs. conventional infusion</td>
<td>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</td>
</tr>
<tr>
<td>Keuleers 2011</td>
<td>Retrospective, n=31 PVT:</td>
<td>Contraindications</td>
<td>Surgery (n=18) compared</td>
<td>Surgery: 2 (11%) perioperative deaths,</td>
<td>Small numbers, no data on</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Type</td>
<td>Patient Population</td>
<td>Intervention vs. Comparator (n)</td>
<td>Outcomes</td>
<td>Study Limitations</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>(179) 21211605</td>
<td>nonrandomized, single center, 1988–2008</td>
<td>MVR=17 (55%), AVR=8 (26%), TVR=6 (19%).</td>
<td>to FT (n=13)</td>
<td>2 (11%) recurrent PVT (follow-up 76 mo)</td>
<td>Thrombus size</td>
</tr>
<tr>
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<td>8 (61%) with restoration of normal valve function.</td>
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<td>4 (31%) recurrent PVT (follow-up 18 mo)</td>
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<td>4 (31%) major complications (death, stroke, TIA, or bleeding requiring surgery)</td>
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</tr>
<tr>
<td>(66) 23489534</td>
<td>Observational, single center clinical experience, 1993–2009</td>
<td>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).</td>
<td>Contraindications to FT, asymptomatic PVT with normal valve hemodynamics and no TE or with, thrombus size &lt;10 mm.</td>
<td>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</td>
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<td>Overall success 68.8% 85.4% 75% 81.5% 85.5% 0.46</td>
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<td></td>
<td>Major nonfatal comp. 12.5% 12.2% 8.3% 11.1% 4.8% NS</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Death 12.5% 2.4% 16.7% 3.7% 0% 0.01</td>
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<td>Multivariate predictors of mortality plus major nonfatal complications: Any thrombolytic therapy regimen other than Group V and a history of stroke/TIA,</td>
<td></td>
</tr>
<tr>
<td>(180) 23329151</td>
<td>Meta-analysis</td>
<td>Published articles on left-sided PVT with at least 5 pts each treated with surgery and FT</td>
<td>Lack of data on primary outcome (restoration of normal valve function)</td>
<td>7 studies with 690 episodes of left sided PVT, 446 treated with surgery, and 244 with FT.</td>
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<td>Outcomes</td>
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<td></td>
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<td>N=446</td>
<td>N=244</td>
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<td></td>
<td>Restored valve Fx 86.5% 69.7% 2.53, 95% CI: 0.94–6.78 0.066</td>
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<tr>
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<td>Death 13.5% 9% 1.95, 95% CI: 0.63–5.98 0.244</td>
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<td></td>
<td>Thromboembolism 1.6% 16% 0.10, 95% CI: 0.04–0.24 &lt;0.001</td>
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<tr>
<td></td>
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<td></td>
<td>Major Bleeding 1.4% 5% 0.27, 95% CI: 0.08–0.98 0.046</td>
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<td></td>
<td>Recurrent PVT 7.1% 25.4% 0.25, 95% CI: 0.08–0.74 0.013</td>
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</tr>
</tbody>
</table>

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.
## Data Supplement 23. Paravalvular Regurgitation (Section 11.8.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Endpoints</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orszulak 1983 (181) 8660002</td>
<td>To report outcome with surgical reoperation for PVR</td>
<td>Retrospective N=105</td>
<td>Surgical reoperative repair of prosthetic PVR</td>
<td>Aortic PVR (n=75) and mitral PVR (n=29)</td>
<td>Early mortality for entire cohort: 5.7%. 5-y survival was 94% for aortic PVR pts and 75% for mitral PVR pts.</td>
<td>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.</td>
</tr>
<tr>
<td>Miller 1995 (182) 8556176</td>
<td>To identify clinical features that predict occurrence of PVR. Outcome after surgical repair also reported</td>
<td>Retrospective N=30</td>
<td>Surgical reoperative repair of aortic prosthetic PVR</td>
<td>Aortic prosthetic PVR</td>
<td>30-d survival=80%; 5-d survival=73%</td>
<td>Prosthesis replacement in 26, suture repair in 4. Trivial or no residual regurgitation in 16 of 20 with echocardiography in follow-up.</td>
</tr>
<tr>
<td>Akins 2005 (183) 16359061</td>
<td>To examine acute and long-term outcome of surgery for PVR</td>
<td>Retrospective N=136</td>
<td>Surgical reoperative repair of aortic or mitral prosthetic PVR</td>
<td>Mitral PVR in 68% Aortic PVR in 32%</td>
<td>Operative mortality, 6.6% Perioperative stroke, 5.1% 10-y survival, 30%</td>
<td>Primary repair in 48%, prosthesis replacement in 52%</td>
</tr>
<tr>
<td>Pate 2006 (184) 16909856</td>
<td>To describe outcome in series of pts undergoing percutaneous repair of PVR</td>
<td>Retrospective N=10 (10 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=9) and aortic PVR (n=1); 9 were not surgical candidates</td>
<td>7 with successful procedure 3 pts died at 1 y</td>
<td>4 of 10 required second procedure 6 with sustained improvement in symptoms 1 retroperitoneal bleed 1 device dislodgement</td>
</tr>
<tr>
<td>Shapira 2007 (185) 11479246</td>
<td>To examine the feasibility and early outcome of percutaneous repair of PVR</td>
<td>Retrospective N=11 (13 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=8), aortic PVR (n=1), and both aortic and mitral PVR (n=2)</td>
<td>10 with device deployment 6 with reduction in regurgitation 5 with NYHA improvement by 1 class</td>
<td>Hemolysis improved in 4, worsened in 4, and was unchanged in 2 in early follow-up 3 deaths in follow-up</td>
</tr>
<tr>
<td>Cortes 2008 (186) 18237605</td>
<td>To examine utility of TEE in percutaneous repair of PVR</td>
<td>Retrospective N=27 (27 defects)</td>
<td>TEE before and procedure (n=27) and at follow-up ≥1 mo (n=17)</td>
<td>Mechanical mitral PVR in pts at high risk for surgery</td>
<td>62% with procedure success TEE helped guide procedure and identified variety of complications</td>
<td>N/A</td>
</tr>
<tr>
<td>Ruiz 2011 (187) 22078427</td>
<td>To examine feasibility and efficacy of the percutaneous repair of PVR</td>
<td>Retrospective N=43 (57 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=36), aortic PVR (n=9), and both aortic and mitral PVR (n=2)</td>
<td>Device deployment success in 86% of pts and 86% of leaks Survival: 92% at 6 m, 86% at 18 m</td>
<td>12 pts required multiple procedures Reduction in need for transfusions or EPO from 56–5% NYHA class improved by ≥1 in 28/35 pts</td>
</tr>
<tr>
<td>Soraja 2011</td>
<td>To examine the feasibility and</td>
<td>Retrospective</td>
<td>Percutaneous repair of</td>
<td>78% mitral PVR, 22% aortic</td>
<td>Device deployment in 89%</td>
<td>Leaflet impingement in 4.3%</td>
</tr>
<tr>
<td>Study Name, Author, Year</td>
<td>Study Aim</td>
<td>Study Type/Size (N)</td>
<td>Intervention vs. Comparator (n)</td>
<td>Patient Population</td>
<td>Endpoints</td>
<td>Adverse Events</td>
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</tr>
<tr>
<td>(188) 21791673</td>
<td>early outcome of percutaneous repair of PVR</td>
<td>N=115 pts (141 defects)</td>
<td>PVR</td>
<td>Average STS risk score=6.9%</td>
<td>Mild or no residual regurgitation in 77% No procedural death</td>
<td>Procedure time average 147 min and decreased with case experience</td>
</tr>
<tr>
<td>Soraja 2011 (189) 22078428</td>
<td>To determine the long-term clinical efficacy of percutaneous repair of PVR</td>
<td>Retrospective N=126 (154 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>79% mitral PVR, 21% aortic PVR Average STS risk score=6.7%</td>
<td>3-y survival, 64% HF accounted to 37% of deaths; noncardiac cause in 30%</td>
<td>Symptom improvement occurred only in pts with mild or no residual regurgitation Hemolytic anemia persisted in 14 of 29 pts</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Primary Endpoint</th>
<th>Predictors of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jault, 1997 (190)</td>
<td>Identify significant predictors of operative mortality, reoperation, and recurrent IEs</td>
<td>Retrospective single-center surgical cohort study</td>
<td>247</td>
<td>NVE alone; surgery 100%</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>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%.</td>
<td>Increased age, cardiogenic shock at the time of operation, insidious illness, and greater thoracic ratio (&gt;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.</td>
</tr>
<tr>
<td>Castillo, 2000 (191)</td>
<td>To determine the clinical features and long-term prognosis of IE in pts who were not drug users.</td>
<td>Prospective single-center case series</td>
<td>138</td>
<td>NVE 69%, PVE 31%; surgery 51%</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>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 (&gt;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.</td>
<td></td>
</tr>
<tr>
<td>Alexiou, 2000 (192)</td>
<td>Single center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late outcome</td>
<td>Retrospective single-center surgical cohort study</td>
<td>118</td>
<td>NVE 70%, PVE 30%; 100% of pts underwent surgery</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Wallace, 2002 (193)</td>
<td>To identify clinical markers available within the first 48 h of admission that are associated with poor outcome in IE</td>
<td>Retrospective single-center cohort study</td>
<td>208</td>
<td>NVE 68%, PVE 32%; surgery 52%</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy</td>
<td>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%).</td>
<td>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.</td>
</tr>
<tr>
<td>Hasbun, 2003 (194)</td>
<td>To derive and externally validate a prognostic</td>
<td>Retrospective multicenter cohort study</td>
<td>513</td>
<td>Pts with left-sided NVE with current</td>
<td>Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, and LV function</td>
<td>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 categories.</td>
<td>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</td>
</tr>
</tbody>
</table>
### 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Primary Endpoint</th>
<th>Predictors of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12697795</td>
<td>classification system for pts with complicated left-sided native valve IE</td>
<td>Retrospective multicenter cohort study</td>
<td>121</td>
<td>symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings</td>
<td>groups with increasing risk for 6-mo mortality: 5%, 15%, 31%, and 59% (p&lt;0.001). In the validation cohort, a similar risk among the 4 groups was observed: 7%, 19%, 32%, and 69% (p&lt;0.001).</td>
<td>[p=0.01], bacterial etiology other than viridans streptococci [p&lt;0.001 except S. aureus, p=0.004], and medical therapy without valve surgery [p=0.002]</td>
<td></td>
</tr>
<tr>
<td>Vikram, 2003 (195) 14693873</td>
<td>To determine whether valve surgery is associated with reduced mortality in pts with complicated, left-sided native valve IE</td>
<td>Retrospective multicenter cohort study</td>
<td>513</td>
<td>Pts with left-sided NVE with current surgical intervention in 45%</td>
<td>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&lt;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).</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>19658370</td>
<td>To identify prognostic markers in 104 pts with PVE and the effects of a medical versus surgical strategy outcome in PVE</td>
<td>Retrospective multicenter cohort study</td>
<td>104</td>
<td>PVE pts; surgery 49%</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy</td>
<td>Factors associated with in-hospital death were severe comorbidity (6% of survivors vs. 41% of those who died; p&lt;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 (80% vs. 90%; p=0.05).</td>
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</tr>
<tr>
<td>Revilla, 2005 (196) 15958370</td>
<td>To describe the profile</td>
<td>Prospective</td>
<td>508</td>
<td>NVE 66%, Brucella, Q fever, Legionella, and</td>
<td>Of these 508 episodes, 132 (34%) were electively</td>
<td>Univariate analysis identified renal failure, septic shock,</td>
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</table>


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<table>
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<th>Predictors of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 (197) 17052690</td>
<td>of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality</td>
<td>multicenter cohort study</td>
<td>PVE 34%; surgery studied for the present report</td>
<td>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%).</td>
<td>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.</td>
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<tr>
<td>Hill, 2007 (198) 17158121</td>
<td>Analyze epidemiology, optimal treatment, and predictors of 6-mo mortality in IE</td>
<td>Prospective single-center cohort study</td>
<td>193</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy</td>
<td>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.</td>
<td>S. aureus, contraindication to surgery (present in 50% of deaths).</td>
<td></td>
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<tr>
<td>Remadi, 2007 (199) 17383330</td>
<td>To evaluate the predictors of outcome and to establish whether early surgery is associated with reduced mortality</td>
<td>Prospective multicenter cohort study</td>
<td>116</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Antibiotic treatment.</td>
<td>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&lt;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&lt;0.001).</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Aksoy, 2007 (200) 17205442</td>
<td>To better understand the impact of surgery on the long-term survival of pts with IE</td>
<td>Prospective single-center cohort study with propensity score matching</td>
<td>426</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Pts' propensities for surgery</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tleyjeh, To examined the Matched</td>
<td>Matched</td>
<td>NVE alone; Propensity score to undergo valve</td>
<td>546</td>
<td>Death occurred in 99 of the 417 pts (23.7%) in the</td>
<td>After adjustment for early (operative) mortality, surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**2014 Valvular Heart Disease Guideline Data Supplements**

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Primary Endpoint</th>
<th>Predictors of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 (201) 17372170</td>
<td>association between valve surgery and all-cause 6 mo mortality among pts with left-sided IE</td>
<td>propensity analysis</td>
<td>surgery 24%</td>
<td>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.</td>
<td>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.</td>
<td>was not associated with a survival benefit (adjusted HR: 0.92; 95% CI: 0.48–1.76).</td>
<td></td>
</tr>
<tr>
<td>Tleyjeh, 2008 (202) 18308866</td>
<td>To examine the association between the timing of valve surgery after IE diagnosis and 6-mo mortality among pts with left-sided IE</td>
<td>Retrospective single-center cohort propensity analysis</td>
<td>NVE alone; surgery 24%</td>
<td>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).</td>
<td>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.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Thuny, 2009 (203) 19329497</td>
<td>To determine whether the timing of surgery could influence mortality and morbidity in pts with complicated IE</td>
<td>Retrospective single-center cohort propensity analysis</td>
<td>NVE 82%, PVE 18%; surgery 100%</td>
<td>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 &quot;&lt;1st wk surgery group&quot; and the &quot;&gt;1st wk surgery group&quot;. The impact of the timing of surgery on 6 mo mortality, relapses, and PVD was analyzed using PS analyses.</td>
<td>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).</td>
<td>Very early surgery (&lt;7 d) associated with improved survival (especially in highest risk pts), but greater likelihood of relapse or post-operative valve dysfunction.</td>
<td></td>
</tr>
<tr>
<td>Manne, 2012 (204)</td>
<td>Describe the morbidity and mortality associated</td>
<td>Retrospective single-center surgical</td>
<td>NVE 58%, PVE 42%, surgery 100%</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography</td>
<td>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%).</td>
<td>Pts with IE caused by S. aureus had significantly higher hospital mortality (15% vs. 8.4%; p&lt;0.05), 6 mo mortality (23% vs. 15%; p=0.05), and 1 y mortality (28% vs. 23%; p=0.05).</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**

- **PS:** Propensity score
- **HR:** Hazard ratio
- **CI:** Confidence interval
- **AHR:** Adjusted hazard ratio
- **OR:** Odds ratio
- **CI:** Confidence interval
<table>
<thead>
<tr>
<th>Author/Year</th>
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</thead>
<tbody>
<tr>
<td>22206953</td>
<td>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</td>
<td>cohort study</td>
<td>22206953</td>
<td>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</td>
<td>data, and treatment strategy</td>
<td>p&lt;0.01, but long-term survival was not significantly different (35% vs. 29%; p=0.19).</td>
<td>vs. 18%, p=0.02) compared with non-S. aureus IE.</td>
</tr>
<tr>
<td>Kang, 2012 (205) 22738096</td>
<td>To compare clinical outcomes of early surgery and conventional treatment in pts with IE</td>
<td>Prospective randomized trial at 2 centers with intention to treat analysis</td>
<td>76</td>
<td>Left-side NVE and high risk of embolism to early surgery (49%) vs. conventional treatment (51%)</td>
<td>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.</td>
<td>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 endpoint 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).</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.
### Data Supplement 25: Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated with Warfarin or Unfractionated Heparin (UFH) (Section 13.3.2)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Aim</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Study Type</th>
<th>Type of Anticoagulation</th>
<th>Endpoints</th>
<th>Summary</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chan, 2000</strong> (206) 10447757</td>
<td>Systematic review anticoagulation mechanical valves</td>
<td>1,234 pregnancies in 976 women</td>
<td>All pts with mechanical prostheses—40 articles—treated with differing anticoagulation regimens 1966–1997</td>
<td>Systematic review of literature</td>
<td>1. Warfarin throughout  2. UFH 1st trimester, then warfarin  3. UFH throughout pregnancy  4. No AC</td>
<td>Maternal Death  1. 1.8%  2. 4.2%  3. 15%  4. 4.7%  Thromboembolic  1. 3.9%  2. 9.2%  3. 33%  4. 24%</td>
<td>Fetal anomalies  1. 6.4%  2. 3.4%  3. 0%  4. 3.3%  Fetal wastage  1. 33%  2. 26%  3. 43%  4. 20%</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Meschengieser, 1999</strong> (207) 10377303</td>
<td>Single center experience anticoagulation mechanical valves</td>
<td>92 pregnancies in 59 women</td>
<td>Consecutive unselected pregnancies between 1986–1997</td>
<td>Observational</td>
<td>1. Warfarin throughout pregnancy  2. UFH 1st trimester, then warfarin  3. UFH throughout pregnancy  4. No A/C</td>
<td>Thromboembolic  1. 0.3 episodes/100 pt mo  2. 4.9 episodes/100 pt mo</td>
<td>Fetal wastage  1. 25%  2. 19%</td>
<td>Reduction of thromboembolic events for mother greatest with warfarin throughout pregnancy. No maternal deaths or valve thrombosis occurred in this study.</td>
</tr>
<tr>
<td><strong>Vitale, 1999</strong> (208) 10334435</td>
<td>Single center experience anticoagulation mechanical valves</td>
<td>58 pregnancies in 43 pts</td>
<td>Consecutive unselected pregnancies between 1987–1997</td>
<td>Observational</td>
<td>Warfarin throughout pregnancy:  A. Dose &lt;5 mg vs. B. Dose &gt;5 mg</td>
<td>Maternal Death  None  Valve thrombosis  2 pts</td>
<td>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)</td>
<td>First to show that fetal complications are dose-dependent, relatively safe if dose ≤5 mg</td>
</tr>
<tr>
<td><strong>Salazar, 1996</strong> (209) 8636556</td>
<td>Single center experience anticoagulation mechanical valves</td>
<td>40 pregnancies in 37 pts</td>
<td>Single center experience of a prospective protocol using UFH SQ during the 1st trimester</td>
<td>Prospective cohort trial</td>
<td>All pts had SQ UFH from 6–12 wk and then during the last 2 wks of gestation</td>
<td>2 cases of massive thrombosis of a MVR tilting disk.  1 death from GI bleeding during warfarin.</td>
<td>37% spontaneous abortion  2.5% neonatal death  No embrophyathy</td>
<td>UFH is a poor anticoagulant and does not prevent massive thrombosis</td>
</tr>
<tr>
<td><strong>Sbarouni, 1994</strong> (210) 8130033</td>
<td>Questionnaire to all cardiac centers in Europe</td>
<td>214 pregnancies in 182 pts (133 with</td>
<td>Questionnaire sent 1994 to all cardiac centers in Europe</td>
<td>Questionnaire data</td>
<td>N/A</td>
<td>6 maternal deaths (4 valve thrombosis, 1 cerebral embolism, 1 pulmonary edema)</td>
<td>No embryopathies in 36 women on warfarin</td>
<td>Heparin is neither effective or safe for both fetus and mother with increased risk of thromboembolism and bleeding</td>
</tr>
</tbody>
</table>
## 2014 Valvular Heart Disease Guideline Data Supplements

<table>
<thead>
<tr>
<th>Author, Year</th>
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<th>Study Size (N)</th>
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<th>Endpoints</th>
<th>Summary</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Lawati 2002 (211) 12142189</td>
<td>Single center experience anticoagulation mechanical valves from country of Oman</td>
<td>63 pregnancies in 21 pts</td>
<td>Consecutive unselected pregnancies between 1983–1997</td>
<td>Observational</td>
<td>1. Warfarin throughout 2. UFH 1st trimester, then Warfarin</td>
<td>Thrombosis of valves 1. None 2. 2 pts</td>
<td>Fetal complications 1. 74% live babies 2. 71% live babies 3. Spontaneous abortion 1. 26% 2. 14% No embryopathy (2 pts with 6 mg, rest with ≤5 mg)</td>
<td>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.</td>
</tr>
<tr>
<td>Sadler 2000 (212) 10688509</td>
<td>Historical cohort of women with mechanical, bioprosthetic and homograft valves from New Zealand</td>
<td>147 pregnancies in 79 pts</td>
<td>All women in New Zealand who had valve replacement 1972–1992 and had subsequent pregnancy</td>
<td>Observational</td>
<td>1. Warfarin throughout pregnancy 2. Warfarin for 6 wk then subq UFH 3. Warfarin for 28 wk then subq UFH</td>
<td>Valve thrombosis 1. 0% 2. 20% 3. 0% Embolic events 1. 0% 2. 20% 3. 25% Hemorrhage 1. 3% 2. 30% 3. 26%</td>
<td>Pregnancy loss 1. 70% 2. 22% 3. 33%</td>
<td>Warfarin had high rate of fetal loss High rate of thromboemboli on heparin (29%) Bioprosthesis or homografts were associated with successful pregnancies</td>
</tr>
<tr>
<td>De Santo 2005 (213) 15999035</td>
<td>Single center experience of all pts who had mechanical prosthesis and became pregnant</td>
<td>48 pregnancies in 37 pts</td>
<td>All women from a single center who had MVR 1975 to 2002 and had subsequent pregnancy</td>
<td>Observational</td>
<td>1. Warfarin throughout A. Dose ≤5 mg B. Dose &gt;5 mg 2. 2 pts with UFH</td>
<td>2/2 pts with UFH had valve thrombosis No pt with warfarin had adverse cardiac or valve related event</td>
<td>1A. 2/23 (8.8%) adverse fetal event 1B. 17/21 (81%) adverse fetal event</td>
<td>If continue warfarin throughout pregnancy, there are no maternal events Adverse fetal events mainly if dose &gt;5 mg</td>
</tr>
</tbody>
</table>
2014 Valvular Heart Disease Guideline Data Supplements

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)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Aim</th>
<th>Study Size (N)</th>
<th>Type of Anticoagulant</th>
<th>Patient Population</th>
<th>Study Type</th>
<th>Endpoints</th>
<th>Summary</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowan, 2001 (214) 11968791</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy</td>
<td>14 pregnancies in 11 women</td>
<td>LMWH throughout pregnancy</td>
<td>All pts with mechanical prosthesis treated with LMWH single center—1997–1999—fixed dose LMWH</td>
<td>Observational</td>
<td>One valve thrombosis 14.3% hemorrhage</td>
<td>9 live births 3 miscarriages 2 terminations</td>
<td>Can achieve successful pregnancy using LMWH throughout pregnancy, but risk of valve thrombosis</td>
</tr>
<tr>
<td>James, 2006 (215) 16966122</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy</td>
<td>75 pregnancies</td>
<td>LMWH throughout pregnancy</td>
<td>Medline search of 73 cases 1966–2006 and 3 of single center using LMWH throughout pregnancy</td>
<td>Meta-analysis</td>
<td>22% thrombotic events 4% maternal mortality</td>
<td>No congenital anomalies 8 spontaneous abortions</td>
<td>Use of LMWH during pregnancy associated with high risk of life threatening thrombosis</td>
</tr>
<tr>
<td>Abildgaard, 2009 (216) 19162303</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy</td>
<td>12 pregnancies in 12 women</td>
<td>LMWH throughout pregnancy</td>
<td>All pts with mechanical prosthesis treated with LMWH throughout pregnancy in country Norway—1997–2008—use anti-Xa levels</td>
<td>Observational</td>
<td>1 systemic embolism and 1 valve thrombosis (both subtherapeutic doses) Pooled risk of thromboembolism 7.1% vs. prior data 25% with UFH</td>
<td>13 healthy babies</td>
<td>No anti-Xa levels performed. Meta-analysis only</td>
</tr>
<tr>
<td>Oran, 2004 (217) 15467905</td>
<td>Meta-analysis of pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens, including LMWH</td>
<td>10 reports (2 prospective) 81 pregnancies in 75 women</td>
<td>LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy</td>
<td>Medline search of studies in pts with prostheses receiving LMWH from 1989–2004</td>
<td>Meta-analysis</td>
<td>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</td>
<td>All thromboemboli occurred in pts with mitral prosthesis who had LMWH throughout pregnancy. Anti Xa levels were not monitored in 90% of thromboembolic events.</td>
<td>Meta-analysis only</td>
</tr>
<tr>
<td>McLintock, 2009 (218) 19661850</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens including LMWH</td>
<td>47 pregnancies in 31 women</td>
<td>Warfarin throughout pregnancy vs. LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy</td>
<td>All pts with mechanical prosthesis treated with differing anticoagulation regimens including LMWH—2 centers—1997–2008—use anti-Xa levels</td>
<td>Observational</td>
<td>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</td>
<td>Poor compliance or subtherapeutic anti-Xa levels were present in all valve thrombosis on LMWH</td>
<td>Retrospective review of small number pts</td>
</tr>
<tr>
<td>Author, Year</td>
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<tr>
<td>Yinon, 2009 (219) 19840573</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy</td>
<td>23 pregnancies in 17 women</td>
<td>LMWH throughout pregnancy</td>
<td>All pts with mechanical prosthesis treated with LMWH—single center 1998–2008—use anti-Xa levels</td>
<td>Observational</td>
<td>1 (4%) maternal thrombosis died 5 (22%) pulmonary edema, arrhythmias, and endocarditis 13% postpartum hemorrhage</td>
<td>19 live births 2 first trimester miscarriages 2 intrauterine deaths</td>
<td>Even with careful monitoring of anti-X-a levels thrombosis may occur, even with low risk AVR</td>
</tr>
<tr>
<td>Quinn, 2009 (220) 19880782</td>
<td>Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy</td>
<td>12 pregnancies in 11 women</td>
<td>LMWH throughout pregnancy</td>
<td>All pts with mechanical prosthesis treated with LMWH—single center—2001–2007—use anti-Xa levels</td>
<td>Observational</td>
<td>3 major bleeds 3 minor bleeds BS MVR thrombosis 1 pt (Xa level not done and later subtherapeutic)</td>
<td>11/12 live births</td>
<td>Increasing dose LMWH during pregnancy necessary Only valve thrombosis occurred in pt with subtherapeutic level Xa</td>
</tr>
</tbody>
</table>

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.
### Prognostic Significant of AF at Time of Surgery

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study “Intervention” Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eguchi et al 2005 (221) 15845559</td>
<td>Examine impact of preoperative AF on outcome of MV repair for 1° MR</td>
<td>Retrospective observational</td>
<td>283 pts with moderate-to-severe MR who underwent MV repair between 1991 and 2002</td>
<td>129 in AF Age 59±13 y 60% male</td>
<td>154 in NSR Age 52±14 y 67% male</td>
<td>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&lt;0.001)</td>
</tr>
<tr>
<td>Alexiou 2007 (222) 17280837</td>
<td>Impact of preoperative AF on early and late outcome after MV repair</td>
<td>Retrospective observational</td>
<td>349 pts undergoing MV repair for primary MR</td>
<td>152 (44%) in AF</td>
<td>197 (56%) in NSR</td>
<td>Kaplan-Meier survival at 7 y was 75±6% for AF pts vs. 90±3% (p=0.005) for SR pts.</td>
</tr>
<tr>
<td>Ngaage 2006 (223) 17643612</td>
<td>Prognostic significance of preoperative AF at the time of AVR</td>
<td>Retrospective observational, cohort comparison</td>
<td>381 AVR 1993 and 2002 matched for age, gender, and LVEF</td>
<td>Preoperative AF (n=129)</td>
<td>Preoperative NSR (n=252)</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Predictors of Return of Sinus Rhythm After Valve Surgery

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study “Intervention” Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua 1994 (224) 8302059</td>
<td>Determine frequency of reversion to NSR after MV repair among pts with preoperative AF</td>
<td>Retrospective, observational</td>
<td>323 consecutive pts who underwent surgical MV valvuloplasty for MR from 1980–1991</td>
<td>97 in AF before surgery</td>
<td>216 in NSR before surgery</td>
<td>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&lt;0.01)</td>
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<tr>
<td>Obadia 1997 (225) 9270633</td>
<td>Determine predictors for return to NSR after MVR</td>
<td>Retrospective, observational</td>
<td>191 pts undergoing surgery for MVR</td>
<td>Preoperative AF in 96 (50%)</td>
<td>Preoperative NSR in 95 (40%)</td>
<td>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 &gt;1 y</td>
</tr>
<tr>
<td>Jessurun 2000 (226) 10814915</td>
<td>Outcome analysis of arrhythmias after MV surgery</td>
<td>Retrospective, observational</td>
<td>162 consecutive pts undergoing MV surgery between 1990 and 1993</td>
<td>Preoperative chronic AF in 74 (46%) and paroxysmal AF in 25 (16%)</td>
<td>Preoperative NSR in 59 (36%)</td>
<td>NSR present postop in 40 of 57 (7%) pts with preop NSR. AF present postop in 58 of 68 (85%) of pts with preop chronic AF (&gt;1 y). NSR present postop in 10 of 29 (34%) pts with preoperative paroxysmal AF.</td>
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### Outcomes With Surgical Maze for AF

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<tr>
<th>Author, Year</th>
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<th>Study Size (N)</th>
<th>Study “Intervention” Group (n)</th>
<th>Study Comparator Group (n)</th>
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<tr>
<td>Deneke 2002 (227) 11922646</td>
<td>Efficacy of a modified maze procedure in pts with chronic AF undergoing MV</td>
<td>Prospective randomized</td>
<td>30 consecutive pts undergoing MVR</td>
<td>Modified maze at time of MVR</td>
<td>MVR alone</td>
<td>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 (0.287) (p&lt;0.01)</td>
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<tr>
<td>Author, Year</td>
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<td>Study Type</td>
<td>Study Size (N)</td>
<td>Study “Intervention” Group (n)</td>
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<tr>
<td>Akpinar 2003</td>
<td>Assess the feasibility and effectiveness of irrigated RF modified maze procedure through a port access approach during MV surgery</td>
<td>Prospective randomized</td>
<td>67 pts with chronic AF eligible for port access MV surgery</td>
<td>33 irrigated RF modified Maze procedure</td>
<td>34 valve procedure alone</td>
<td>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.</td>
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<tr>
<td>Jessarun 2003</td>
<td>Assess outcome of combining the Maze III procedure with MV surgery</td>
<td>Prospective, randomized (2:5:1 ratio)</td>
<td>35 pts with AF undergoing MVR. Mean age 64 y</td>
<td>Maze III in 25</td>
<td>MVR along in 10</td>
<td>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.</td>
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<tr>
<td>Abreu Filho 2005</td>
<td>Evaluate effectiveness of maze procedure for permanent AF in pts with rheumatic MV disease</td>
<td>Prospective randomized</td>
<td>70 consecutive pts (2002–03) with rheumatic MV disease and permanent AF</td>
<td>MV surgery plus Maze III procedure saline-Irrigated cooled-tip RF ablation</td>
<td>MV surgery alone</td>
<td>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).</td>
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<tr>
<td>Doukas 2005</td>
<td>To determine whether intraoperative RF ablation increases the long-term restoration of NSR and improves exercise capacity</td>
<td>Randomized, double-blind trial</td>
<td>97 pts referred for MV surgery with AF for at least 6 mo</td>
<td>MV surgery plus RF left atrial ablation</td>
<td>MV surgery alone</td>
<td>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&lt;0.001</td>
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<tr>
<td>Von Oppell 2009</td>
<td>Evaluate the effect of maze procedure on postop AF in pts undergoing MV surgery</td>
<td>Prospective randomized</td>
<td>49 pts undergoing MV surgery with AF of more than 6 mo duration in 2004–06</td>
<td>MV surgery plus RF maze procedure (n=24)</td>
<td>MV surgery plus intensive rhythm control strategy (n=25).</td>
<td>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).</td>
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<tr>
<td>Cheng 2010</td>
<td>To determine if surgical maze ablation for AF improves clinical outcomes and resource utilization</td>
<td>Meta-analysis</td>
<td>4647</td>
<td>Adults with persistent and permanent AF undergoing maze surgical ablation at the time of cardiac surgery</td>
<td>Persistent or permanent AF undergoing cardiac surgery without maze procedure</td>
<td>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).</td>
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<tr>
<td>Bando 2003</td>
<td>Identify risk factors for mortality and stroke after mechanical MVR</td>
<td>Retrospective</td>
<td>812 pts undergoing MVR between 1977–2001. Chronic AF present in 630 (78%)</td>
<td>In addition to MVR: 403 (61%) had LV appendage closure 148 (18%) had LA plication 185 (23%) had maze procedure 348 (43%) had tricuspid</td>
<td></td>
<td>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 (88%, p&lt;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=0.001) and omission of the maze procedure (OR: 3.40; 95% CI: 1.14–10.14; p=0.003) were significant risk factors for</td>
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### 2014 Valvular Heart Disease Guideline Data Supplements

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<th>Study Comparator Group (n)</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Bum Kim 2012 (235) 234</td>
<td>Evaluate long-term benefits of the maze procedure in pts with chronic AF undergoing mechanical MVR</td>
<td>Retrospective, observational</td>
<td>569 pts undergoing mechanical MVR between 1997−2010</td>
<td>317 with MVR plus a concomitant maze procedure</td>
<td>252 with MVR alone</td>
<td>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</td>
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<tr>
<td>Malaisrie 2012 (236) 235</td>
<td>Determine the impact of concomitant AF ablation in pts undergoing AVR</td>
<td>Retrospective, observational</td>
<td>124 pts (mean age 74±12 y) with pre-existing AF undergoing AVR</td>
<td>80 (65%) had concomitant surgical AF ablation</td>
<td>44 had AVR alone</td>
<td>Postop freedom from AF when not receiving anti-arrhythmic drugs occurred in 58 pts (62%) in the ablation group, compared to 8 (36%) in the nonablation group (p&lt;0.001)</td>
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<tr>
<td>Liu 2010 (237) 236</td>
<td>Compare pulmonary vein isolation versus maze procedure for treatment of permanent AF</td>
<td>Prospective randomized</td>
<td>99 with rheumatic heart disease and permanent AF</td>
<td>49 with valve surgery plus circumferential pulmonary vein isolation</td>
<td>50 with valve surgery plus maze procedure for AF</td>
<td>After one procedure, pts undergoing the maze procedure had a significantly higher freedom from atrial arrhythmias (82% vs. 55.2%, p&lt;0.001). At 15–20 mo follow-up, cumulative rates of sinus rhythm were 71% vs. 88% (p&lt;0.001).</td>
</tr>
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</table>

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)

<table>
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<tr>
<th>Study Name, Author, Year</th>
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<th>Study Type</th>
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<th>Predictors of Adverse Outcomes</th>
<th>Study Limitations</th>
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<td>Aortic Stenosis</td>
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<tr>
<td>Agarwal 2013 (238) 23481524</td>
<td>Compared outcomes with noncardiac surgery in pts with moderate vs. severe AS.</td>
<td>Retrospective surgical and echocardiographic database</td>
<td>634 pts with AS; 244 with severe AS and 390 with moderate AS</td>
<td>2,536 controls without AS propensity matched for 6 revised cardiac risk index criteria plus age and sex.</td>
<td>Severe AS defined as valve area &lt;1 cm². Moderate AS as valve area 1.0–1.5 cm².</td>
<td>Emergency surgery.</td>
<td>Combined primary endpoint of 30-d mortality plus MI occurred in 4.9% of pts with AS vs. 2.1% in controls (p&lt;0.001)</td>
<td>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).</td>
</tr>
<tr>
<td>Calleja 2010 (239) 20381670</td>
<td>Evaluate post-op outcomes of pts with asymptomatic, severe AS</td>
<td>Retrospective</td>
<td>30 pts with asymptomatic severe AS undergoing noncardiac surgery.</td>
<td>2,536 controls without AS propensity matched for 6 revised cardiac risk index criteria plus age and sex.</td>
<td>Noncardiac surgery, intermediate risk severe AS vs. mild or moderate AS=77% vs. 83%, ASA 3=63% vs. 62%, general anesthesia=73% vs. 82%.</td>
<td>AR &gt;moderate, symptomatic AS.</td>
<td>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</td>
<td>Hypotension AS severe: 9/30 (30%) vs. AS mild/moderate: 10/60 (17%); p=0.11.</td>
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<tr>
<td>Leibowitz 2009 (240) 19287130</td>
<td>Outcome of pts with AS undergoing hip fracture repair</td>
<td>Retrospective</td>
<td>Pts with AS (n=32) Age-matched control (n=88) Elderly pts &gt;70 y, with AVA &lt;1 cm²</td>
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<tr>
<td>Zahid 2005 (241) 16054477</td>
<td>Evaluate the perioperative risk of noncardiac surgery in pts with AS</td>
<td>Retrospective Based on National Hospital Discharge Survey</td>
<td>AS=3,149</td>
<td>AS-no=10,284 age/surgical risk matched</td>
<td>Noncardiac surgery (1996–2002)</td>
<td>Cardiac surgery</td>
<td>The presence of AS is not a significant predictor for mortality after adjusting for all significant univariable predictor of in-hospital death.</td>
<td>The presence of AS increased the likelihood of AMI (3.86% in AS vs. 2.03% in controls,</td>
</tr>
<tr>
<td>Torsher 1998</td>
<td>Outcomes of pts with AS</td>
<td>Retrospective</td>
<td>Severe AS=19 N/A</td>
<td>Noncardiac N/A</td>
<td>In selected pts with severe AS, the risk of noncardiac</td>
<td>N/A</td>
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<tr>
<td>Study Name, Author, Year</td>
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<tr>
<td>(242) 9485135</td>
<td>undergoing noncardiac surgery</td>
<td>Case-control</td>
<td>14 pts with mild MR</td>
<td>NA</td>
<td>Undergoing noncardiac surgery</td>
<td>Tracheal intubation prior to noncardiac surgery</td>
<td>Intraoperative course had frequent (31%) minor complications: controllably hypotension and bradycardia</td>
<td>Post-op complications were serious: Death=11.9%, MI=0, V/tach/fib=4.8%, pulmonary edema=23.8%</td>
</tr>
<tr>
<td>Lai 2007 (243) 17363316</td>
<td>Perioperative outcome of pts with MR undergoing noncardiac surgery</td>
<td>Retrospective</td>
<td>94 pts with moderate-severe MR</td>
<td>NA</td>
<td>Undergoing noncardiac surgery</td>
<td>Tracheal intubation prior to noncardiac surgery</td>
<td>Intraoperative course had frequent (31%) minor complications: controllably hypotension and bradycardia</td>
<td>Post-op complications were serious: Death=11.9%, MI=0, V/tach/fib=4.8%, pulmonary edema=23.8%</td>
</tr>
<tr>
<td>Lai 2010 (244) 17930243</td>
<td>Perioperative outcome of chronic, moderate-severe AR who undergo noncardiac surgery</td>
<td>Retrospective (1999–2006)</td>
<td>Chronic, moderate-severe AR=167</td>
<td>Case-matched=167</td>
<td>Chronic moderate-severe AR</td>
<td>Prolonged intubation and acute pulmonary edema: 16.2% vs. 5.4%; p=0.003, Death: AR=9% vs. 1.8%; p=0.008</td>
<td>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</td>
<td>N/A</td>
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</tbody>
</table>

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.
References


2014 Valvular Heart Disease Guideline Data Supplements


## 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (February 2014)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speaker’s Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
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<tr>
<td>Rick Nishimura, (Co-Chair)</td>
<td>Mayo Clinic, Division of Cardiovascular Disease—Judd and Mary Morris Leighton Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Catherine M. Otto, (Co-Chair)</td>
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<tr>
<td>Robert O. Bonow</td>
<td>Northwestern University Medical School—Goldberg Distinguished Professor</td>
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<td>• Society for Heart Valve Disease†</td>
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<tr>
<td>Blase A. Carabello</td>
<td>VA Medical Center—Professor of Medicine, Baylor College of Medicine</td>
<td>None</td>
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<tr>
<td>John P. Erwin III</td>
<td>Scott and White Hospital and Clinic—Senior Staff Cardiologist, Associate Professor of Medicine</td>
<td>None</td>
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<td>Robert A. Guyton</td>
<td>Emory Clinic, Inc.—Professor and Chief, Division of Cardiothoracic Surgery</td>
<td>• Medtronic</td>
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<td>None</td>
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<td>Patrick T. O’Gara</td>
<td>Brigham and Women’s Hospital—Professor of Medicine; Harvard</td>
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<td>• Lantheus Medical Imaging (DSMB)</td>
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<tr>
<th>Medical School—Director of Clinical Cardiology</th>
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<td>Carlos E. Ruiz</td>
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<td>• Anesthesia &amp; Analgesia (Editor)</td>
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<tr>
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<td>Mayo Clinic—Associate Professor of Medicine</td>
<td>None</td>
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<td>• Intellectual property patent on percutaneous closure of paravalvular prosthetic regurgitation</td>
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<td>Thoralf M. Sundt III</td>
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<td>• St. Jude Medical</td>
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<td>James D. Thomas</td>
<td>Cleveland Clinic—Professor of Medicine and Biomedical Engineering</td>
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*Significant relationship.
†No financial benefit.

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