

ACC/AHA CLINICAL PRACTICE GUIDELINE

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

WRITING COMMITTEE MEMBERS*

Catherine M. Otto, MD, FACC, FAHA, Co-Chair
Rick A. Nishimura, MD, MACC, FAHA, Co-Chair
Robert O. Bonow, MD, MS, MACC, FAHA
Blase A. Carabello, MD, FACC, FAHA
John P. Erwin III, MD, FACC, FAHA
Federico Gentile, MD, FACC
Hani Jneid, MD, FACC, FAHA
Eric V. Krieger, MD, FACC
Michael Mack, MD, MACC
Christopher McLeod, MBChB, PhD, FAHA
Patrick T. O’Gara, MD, MACC, FAHA†
Vera H. Rigolin, MD, FACC, FAHA
Thoralf M. Sundt III, MD, FACC, FAHA
Annemarie Thompson, MD
Christopher Toly

Developed in collaboration with and endorsed by 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

ACC/AHA Joint Committee on Clinical Practice Guidelines Members, see page e184

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■ mitral regurgitation ■ mitral stenosis
■ mitral transcatheter edge-to-edge repair ■ prosthetic valve
■ pulmonic regurgitation ■ pulmonic stenosis ■ transcatheter aortic valve replacement or implantation ■ tricuspid regurgitation ■ tricuspid stenosis
■ valvular heart disease

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information.

†ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison.

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TOP 10 TAKE-HOME MESSAGES

1. Disease stages in patients with valvular heart disease should be classified (Stages A, B, C, and D) on the basis of symptoms, valve anatomy, the severity of valve dysfunction, and the response of the ventricle and pulmonary circulation.
2. In the evaluation of a patient with valvular heart disease, history and physical examination findings should be correlated with the results of noninvasive testing (ie, ECG, chest x-ray, trans-thoracic echocardiogram). If there is discordance between the physical examination and initial noninvasive testing, consider further noninvasive (computed tomography, cardiac magnetic resonance imaging, stress testing) or invasive (transesophageal echocardiography, cardiac

catheterization) testing to determine optimal treatment strategy.

3. For patients with valvular heart disease and atrial fibrillation (except for patients with rheumatic mitral stenosis or a mechanical prosthesis), the decision to use oral anticoagulation to prevent thromboembolic events, with either a vitamin K antagonist or a non-vitamin K antagonist anticoagulant, should be made in a shared decision-making process based on the CHA₂DS₂-VASc score. Patients with rheumatic mitral stenosis or a mechanical prosthesis and atrial fibrillation should receive oral anticoagulation with a vitamin K antagonist.
4. All patients with severe valvular heart disease being considered for valve intervention should be evaluated by a multidisciplinary team, with either referral to or consultation with a Primary or Comprehensive Valve Center.
5. Treatment of severe aortic stenosis with either a transcatheter or surgical valve prosthesis should be based primarily on symptoms or reduced ventricular systolic function. Earlier intervention may be considered if indicated by results of exercise testing, biomarkers, rapid progression, or the presence of very severe stenosis.
6. Indications for transcatheter aortic valve implantation are expanding as a result of multiple randomized trials of transcatheter aortic valve implantation versus surgical aortic valve replacement. The choice of type of intervention for a patient with severe aortic stenosis should be a shared decision-making process that considers the lifetime risks and benefits associated with type of valve (mechanical versus bioprosthetic) and type of approach (transcatheter versus surgical).
7. Indications for intervention for valvular regurgitation are relief of symptoms and prevention of the irreversible long-term consequences of left ventricular volume overload. Thresholds for intervention now are lower than they were previously because of more durable treatment options and lower procedural risks.
8. A mitral transcatheter edge-to-edge repair is of benefit to patients with severely symptomatic primary mitral regurgitation who are at high or prohibitive risk for surgery, as well as to a select subset of patients with secondary mitral regurgitation who remain severely symptomatic despite guideline-directed management and therapy for heart failure.
9. Patients presenting with severe symptomatic isolated tricuspid regurgitation, commonly associated with device leads and atrial fibrillation, may benefit from surgical intervention to reduce symptoms and recurrent hospitalizations if done before

the onset of severe right ventricular dysfunction or end-organ damage to the liver and kidney.

10. Bioprosthetic valve dysfunction may occur because of either degeneration of the valve leaflets or valve thrombosis. Catheter-based treatment for prosthetic valve dysfunction is reasonable in selected patients for bioprosthetic leaflet degeneration or paravalvular leak in the absence of active infection.

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations.

Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment.

Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,^{1,2} and on the basis of internal

reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance "user-friendliness." Guidelines are written and presented in a modular "knowledge chunk" format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. Word limit targets and a web supplement for useful but noncritical tables and figures are 2 recent modifications.

In recognition of the importance of cost-value considerations, in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.³

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections or knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual⁴ and other methodology articles.⁵⁻⁷

Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee members have requisite content expertise and are representative of the broader cardiovascular community. Experts are selected across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives or biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found at <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy>. Appendix 1 of the guideline lists writing committee members' relevant RWI; for the purposes of

full transparency, their comprehensive disclosure information is available online (<https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000923>). Comprehensive disclosure information for the Joint Committee is also available at <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces>.

Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.⁴⁻⁵ Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are one or more questions deemed of utmost clinical importance that merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR."

Guideline-Directed Management and Therapy

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

*Patrick T. O'Gara, MD, MACC, FAHA
Chair, ACC/AHA Joint Committee on Clinical Practice Guidelines*

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 March 1, 2020. Searches were extended to studies, reviews, and other evidence involving human subjects that were published in English and indexed in 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, transcatheter aortic valve replacement or implantation, and percutaneous mitral clip. 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 writing committee was composed of clinicians, which included cardiologists, interventionalists, surgeons, anesthesiologists, and a patient representative. Members were required to disclose all RWI relevant to the data under consideration.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and the AHA, as well as content reviewers nominated by the ACC and AHA. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

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 2008.¹ Another full revision was made in 2014,² with an update in 2017.³ There was an additional statement of clarification specifically for surgery for aortic dilation in patients with bicuspid aortic valves (BAV) in 2016.⁴ The present guideline will replace the 2014 guideline and 2017 focused update. Some recommendations from the earlier VHD guidelines have been updated as warranted by new evidence or a better understanding of

Table 1. Associated Guidelines and Related References

Title	Organization	Publication Year (Reference)
Recommendations for Evaluation of the Severity of Native Valvular Regurgitation With Two-Dimensional and Doppler Echocardiography	ASE	2017 ⁵
European Association of Echocardiography Recommendations for the Assessment of Valvular Regurgitation, Part 2: Mitral and Tricuspid Regurgitation (Native Valve Disease)	EAE	2010 ⁶
Guidelines for the Management of Patients With Atrial Fibrillation	ACC/AHA/ESC	2006, 2008, 2019 ⁷⁻⁹
Guidelines for the Management of Adults With Congenital Heart Disease	ACC/AHA	2018 ¹⁰
Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice	EAE/ASE	2009 ¹¹
Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography	EACI/ASE	2017 ¹²
Guidelines for the Evaluation of Valvular Regurgitation After Percutaneous Valve Repair or Replacement: A Report from the American Society of Echocardiography	ASE	2019 ¹³
Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound	ASE	2009 ¹⁴
Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy	ACCF/AHA	2011 ¹⁵ 2020 ¹⁶
Guidelines on the Management of Cardiovascular Diseases During Pregnancy	ESC	2011, 2018 ^{17, 18}
Antithrombotic and Thrombolytic Therapy for Valvular Disease: Antithrombotic Therapy and Prevention of Thrombosis	ACCP	2012 ¹⁹
Guidelines on the Management of Valvular Heart Disease	ESC/EACTS	2012 ²⁰ 2017 ²¹
Guideline for the Management of Heart Failure	ACCF/AHA	2017 ²²

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; AHA, American Heart Association; ASE, American Society of Echocardiography; EACI, European Association of Cardiovascular Imaging; EACTS, European Association of Cardio Thoracic Surgery; EAE, European Association of Echocardiography; and ESC, European Society of Cardiology.

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. Where applicable, sections were divided into subsections of 1) diagnosis and follow-up, 2) medical therapy, and 3) intervention. The purpose of these subsections is to categorize the Class of Recommendation according to the clinical decision-making pathways that caregivers use in the management of patients with VHD.

The document recommends a combination of lifestyle modifications and medications that constitute components of GDMT. For both 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 1 is a list of associated guidelines that may be of interest to the reader.

1.5. Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).¹

1.6. Abbreviations

Abbreviation	Meaning/Phrase
2D	2-dimensional
3D	3-dimensional
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
ARB	angiotensin receptor blocker
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
AS	aortic stenosis
AVR	aortic valve replacement
BAV	bicuspid aortic valve
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CMR	cardiac magnetic resonance
COR	Class of Recommendation
CT	computed tomography
ECG	electrocardiogram
GDMT	guideline-directed management and therapy
HF	heart failure
IE	infective endocarditis
INR	international normalized ratio
LA	left atrium (left atrial)
LMWH	low-molecular-weight heparin

LOE	Level of Evidence
LV	left ventricle (left ventricular)
LVEDD	left ventricular end-diastolic dimension
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic dimension
MDT	multidisciplinary team
MR	mitral regurgitation
MS	mitral stenosis
NOAC	non-vitamin K oral anticoagulant
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PET	positron emission tomography
PMBC	percutaneous mitral balloon commissurotomy
RCT	randomized controlled trial
RV	right ventricle (right ventricular)
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation
TEE	transesophageal echocardiography (echocardiogram)
TEER	transcatheter edge-to-edge repair
TR	tricuspid regurgitation
TTE	transthoracic echocardiography (echocardiogram)
UFH	unfractionated heparin
VHD	valvular heart disease
ViV	valve-in-valve
VKA	vitamin K antagonist

2. GENERAL PRINCIPLES

2.1. Evaluation of the Patient With Known or Suspected Native VHD

Patients with VHD may present with a heart murmur, symptoms, or incidental findings of valvular abnormalities on noninvasive testing. Irrespective of the presentation, all patients with known or suspected VHD should undergo an initial meticulous history and physical examination. A detailed physical examination should be performed to diagnose and assess the severity of valve lesions. An electrocardiogram (ECG) to confirm heart rhythm and a chest x-ray to assess the presence or absence of pulmonary congestion or other lung pathology may be helpful in the initial assessment of patients with known or suspected VHD. A comprehensive transthoracic echocardiogram (TTE) with 2-dimensional (2D) imaging and Doppler interrogation should be performed for diagnosis and evaluation of known or suspected VHD. The TTE also provides additional information, such as the effect of the valve lesion on the cardiac chambers and great vessels, as well as an assessment of other valve lesions. To determine the optimal treatment for a patient with VHD, ancillary testing may be required, such as transesophageal echocardiography

(TEE), computed tomography (CT), cardiac magnetic resonance (CMR) imaging, stress testing, Holter monitoring, diagnostic hemodynamic cardiac catheterization, or positron emission tomography (PET) combined with CT imaging. If intervention is contemplated, surgical or procedural risk should be estimated and other factors also considered, including comorbidities, frailty, and patient preferences and values (Table 3).

2.2. Definitions of Severity of Valve Disease

Classification of valve disease severity is based on multiple criteria, including symptoms, valve anatomy, valve hemodynamics and the effects of valve dysfunction on ventricular and vascular function (eg, end-organ damage). Surgical and transcatheter interventions are performed primarily on patients with severe VHD, but diagnosis, patient education, periodic monitoring, and medical therapy are essential elements in the management of patients at risk of VHD and with mild to moderate valve dysfunction. This document provides a classification of the progression of VHD, with 4 stages (A to D). Indications for intervention and periodic monitoring are dependent on 1) the presence or absence of symptoms, 2) the severity of VHD, 3) the response of the LV and/or RV to volume or pressure overload caused by VHD, and 4) the effects on the pulmonary or systemic circulation (Table 4). The purpose of valvular intervention is to improve symptoms, prolong survival, and minimize the risk of VHD-related complications, such as irreversible ventricular dysfunction, pulmonary hypertension, stroke, and atrial fibrillation (AF). Thus, the criteria for "severe" VHD are based on predictors of clinical outcome from observational studies, registry data, and randomized clinical trials (RCTs) of patients with VHD. Of course, severity is a continuous variable; categorizing disease into stages, from A to D, simply provides a framework, or starting point, for diagnosis and management, and it is recognized that not all patients will fit perfectly into a specific stage. Some patients will have symptoms or end-organ damage with valve hemodynamics that do not quite meet specific disease severity criteria, and numerical measures may not match exactly across all categories. Conversely, other patients may remain asymptomatic without obvious evidence of end-organ damage despite apparently severe VHD. Criteria for the stages of each individual valve lesion are listed in Section 3.1 (Table 13), Section 4.2 (Table 15), Section 6.1 (Table 16), Section 7.2 (Table 17), Section 7.3 (Table 18), and Section 8.1 (Table 20).

2.3. Diagnosis and Follow-Up

2.3.1. Diagnostic Testing: Initial Diagnosis

TTE is the standard diagnostic test in the initial evaluation of patients with known or suspected VHD.¹⁻⁴

Table 2. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE†
CLASS 1 (STRONG) Benefit >>> Risk Suggested phrases for writing recommendations: - Is recommended - Is indicated/useful/effective/beneficial - Should be performed/administered/other - Comparative-Effectiveness Phrases‡: - Treatment/strategy A is recommended/indicated in preference to treatment B - Treatment A should be chosen over treatment B	LEVEL A - High-quality evidence‡ from more than 1 RCT - Meta-analyses of high-quality RCTs - One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) Benefit >> Risk Suggested phrases for writing recommendations: - Is reasonable - Can be useful/effective/beneficial - Comparative-Effectiveness Phrases‡: - Treatment/strategy A is probably recommended/indicated in preference to treatment B - It is reasonable to choose treatment A over treatment B	LEVEL B-R (Randomized) - Moderate-quality evidence‡ from 1 or more RCTs - Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) Benefit ≥ Risk Suggested phrases for writing recommendations: - May/might be reasonable - May/might be considered - Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	LEVEL B-NR (Nonrandomized) - Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies - Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) Benefit = Risk (Generally, LOE A or B use only) Suggested phrases for writing recommendations: - Is not recommended - Is not indicated/useful/effective/beneficial - Should not be performed/administered/other	LEVEL C-LD (Limited Data) - Randomized or nonrandomized observational or registry studies with limitations of design or execution - Meta-analyses of such studies - Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) Risk > Benefit Suggested phrases for writing recommendations: - Potentially harmful - Causes harm - Associated with excess morbidity/mortality - Should not be performed/administered/other	LEVEL C-EO (Expert Opinion) Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

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

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

TTE allows accurate assessment of valve anatomy and etiology, concurrent valve disease, and associated abnormalities, such as aortic dilation. Left ventricular (LV) anatomy and function are characterized by linear dimensions, as well as by 2D and 3D volumes and ejection fraction (LVEF), and it is recognized that decisions are most robust when based on sequential studies, given the inherent measurement variability for these parameters.⁵ Doppler echocardiography provides accurate noninvasive determination of valve hemodynamics.^{1,2,6} For stenotic lesions, key measurements are maximum velocity, mean gradient, and valve area. For regurgitant lesions, calculation of regurgitant orifice area, volume, and fraction is performed, when possible in the context of a multiparameter severity grade based on

color Doppler imaging, continuous- and pulsed-wave Doppler recordings, and the presence or absence of distal flow reversals. Pulmonary systolic pressure also is estimated, along with qualitative evaluation of right ventricular (RV) size and function.⁷ In selected patients, additional testing, such as stress testing, TEE, cardiac catheterization, and CT or CMR imaging, might be indicated. However, both the performance and interpretation of these diagnostic tests require meticulous attention to detail, as well as expertise in cardiac imaging and evaluation of hemodynamics. Because echocardiography remains the mainstay of the initial evaluation of all patients with VHD, it is recommended that the laboratory be an Intersocietal Accreditation Commission (IAC)-accredited program.⁸

Table 3. Evaluation of Patients With Known or Suspected VHD

Reason	Test	Indication
Initial evaluation: All patients with known or suspected valve disease	TTE*	Establishes chamber size and function, valve morphology and severity, and effect on pulmonary and systemic circulation
	History and physical	Establishes symptom severity, comorbidities, valve disease presence and severity, and presence of HF
	ECG	Establishes rhythm, LV function, and presence or absence of hypertrophy
Further diagnostic testing: Information required for equivocal symptom status, discrepancy between examination and echocardiogram, further definition of valve disease, or assessing response of the ventricles and pulmonary circulation to load and to exercise	Chest x-ray	Important for the symptomatic patient; establishes heart size and presence or absence of pulmonary vascular congestion, intrinsic lung disease, and calcification of aorta and pericardium
	TEE	Provides high-quality assessment of mitral and prosthetic valve, including definition of intracardiac masses and possible associated abnormalities (eg, intracardiac abscess, LA thrombus)
	CMR	Provides assessment of LV volumes and function, valve severity, and aortic disease
	PET CT	Aids in determination of active infection or inflammation
	Stress testing	Gives an objective measure of exercise capacity
	Catheterization	Provides measurement of intracardiac and pulmonary pressures, valve severity, and hemodynamic response to exercise and drugs
Further risk stratification: Information on future risk of the valve disease, which is important for determination of timing of intervention	Biomarkers	Provide indirect assessment of filling pressures and myocardial damage
	TTE strain	Helps assess intrinsic myocardial performance
	CMR	Assesses fibrosis by gadolinium enhancement
	Stress testing	Provides prognostic markers
	Procedural risk	Quantified by STS (Predicted Risk of Mortality) and TAVI scores
	Frailty score	Provides assessment of risk of procedure and chance of recovery of quality of life
Preprocedural testing: Testing required before valve intervention	Dental examination	Rules out potential infection sources
	CT coronary angiogram or invasive coronary angiogram	Gives an assessment of coronary anatomy
	CT: Peripheral	Assesses femoral access for TAVI and other transcatheter procedures
	CT: Cardiac	Assesses suitability for TAVI and other transcatheter procedures

*TTE is the standard initial diagnostic test in the initial evaluation of patients with known or suspected VHD.

CMR indicates cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; PET, positron emission tomography; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and VHD, valvular heart disease.

2.3.2. Diagnostic Testing: Changing Signs or Symptoms

Patients with VHD should be instructed to promptly report any change in symptom status. The onset of symptoms or a change in the physical examination should raise concern about the cardiac response to the valve lesion, necessitating a repeat TTE. A repeat comprehensive TTE study can determine whether symptoms are caused by progressive valve dysfunction, deterioration of the ventricular response to the volume or pressure overload, or another etiology. New signs on physical examination also warrant a repeat TTE.¹⁻⁷ This requires that patients with known VHD have access to a primary care provider and a cardiovascular specialist.

2.3.3. Diagnostic Testing: Routine Follow-Up

After initial evaluation of an asymptomatic patient with VHD, the clinician should continue regular follow-up with periodic examinations and TTE. The purpose of follow-up is to prevent the irreversible consequences of severe

VHD, primarily affecting the status of the ventricles and pulmonary circulation, which may occur in the absence of symptoms. At a minimum, a yearly history and physical examination are necessary. The frequency of repeat 2D and Doppler echocardiography is based on the type and severity of the valve lesion, the known rate of progression of the specific valve lesion, and the effect of the valve lesion on the affected ventricle (Table 5).¹⁻¹⁴ Patients with Stages C2 and D disease are not included in this table because they would be considered candidates for intervention. The follow-up interval may be extended in patients with mild regurgitation who show no change over a 10- to 15-year period. In addition to routine periodic imaging, the onset of symptoms or a change in the physical examination should raise concern about the cardiac response to the valve lesion, necessitating a repeat TTE.

2.3.4. Diagnostic Testing: Cardiac Catheterization

Although TTE is now able to provide the required anatomic and hemodynamic information in most

Table 4. Stages of VHD

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

LV indicates left ventricle; RV, right ventricle; and VHD, valvular heart disease.

patients with VHD, there is still a subset of patients in whom hemodynamic catheterization is necessary to ensure that the proper decision about treatment is made. If noninvasive testing yields inconclusive data, particularly in the symptomatic patient, or if there is a discrepancy between the noninvasive tests and clinical findings, a hemodynamic cardiac catheterization with direct intracardiac measurements of transvalvular pressure gradients and cardiac output measurements provides valuable clinical information. Severity of stenosis may be underestimated when imaging is difficult or when the Doppler beam is not aligned parallel to the direction of the high-velocity jet. Severity of valve regurgitation may be overestimated or underestimated if the image or Doppler data quality is suboptimal. Contrast angiography is sometimes useful for a semiquantitative assessment of the severity of regurgitation in those instances in which the noninvasive results are discordant with the physical examination.¹ A major advantage of cardiac catheterization is the measurement of intracardiac pressures and pulmonary vascular resistance, which may further aid in decision-making about valve

intervention. Diagnostic interventions that can be performed in the catheterization laboratory include the use of dobutamine in low-flow states, pulmonary vasodilators in pulmonary hypertension, and exercise hemodynamics in patients with discrepant symptoms.^{1,2} A hemodynamic catheterization needs to be done with meticulous attention to detail by persons with knowledge and expertise in assessing patients with VHD.

2.3.5. Diagnostic Testing: Exercise Testing

In a subset of patients, exercise stress testing will be of additional value in determining optimal therapy. Because of the slow, insidious rate of progression of many valve lesions, patients may deny symptoms as they gradually limit their activity level over several years to match the gradual limitations imposed by the valve lesion. In patients with an equivocal history of symptoms, exercise testing helps identify those who are truly symptomatic.^{1,2} Exercise stress testing (ie, examining the exercise capacity and blood pressure response) is of prognostic value in patients with asymptomatic valve disease and provides further information about the timing of a potential intervention.^{3–11} It is important that exercise testing in patients with severe VHD always be performed by trained operators, with continuous monitoring of the ECG and blood pressure.

2.4. Basic Principles of Medical Therapy

In patients being evaluated for VHD, standard GDMT for cardiac risk factors, including hypertension, diabetes mellitus, and hyperlipidemia, should not be neglected. Heart-healthy lifestyle factors (exercising, consuming a healthy diet, not smoking, and maintaining a normal body size) are no different for patients with VHD than for the general population. Many patients with asymptomatic VHD feel better with regular aerobic exercise to improve cardiovascular fitness.^{1–3} Although heavy isometric repetitive training might increase LV afterload, resistive training with small free weights or repetitive

Table 5. Frequency of Echocardiograms in Asymptomatic Patients With VHD and Normal LV Function

Stage	Type of Valve Lesion			
	Aortic Stenosis*	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Progressive (Stage B)	Every 3–5 y (mild severity; V_{max} 2.0–2.9 m/s)	Every 3–5 y (mild severity)	Every 3–5 y (MV area >1.5 cm ²)	Every 3–5 y (mild severity)
	Every 1–2 y moderate severity; V_{max} 3.0–3.9 m/s)	Every 1–2 y (moderate severity)		Every 1–2 y (moderate severity)
Severe asymptomatic (Stage C1)	Every 6–12 mo (V_{max} ≥4 m/s)	Every 6–12 mo	Every 1–2 y (MV area 1.0–1.5 cm ²)	Every 6–12 mo
		Dilating LV: More frequently	Every year (MV area <1.0 cm ²)	Dilating LV: More frequently

Patients with mixed valve disease may require serial evaluations at intervals earlier than recommended for single-valve lesions. These intervals apply to most patients with each valve lesion and do not take into consideration the etiology of the valve disease.

*With normal stroke volume.

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

Table 6. Secondary Prevention of Rheumatic Fever

Antibiotics for Prevention	Dosage*
Penicillin G benzathine	1.2 million U intramuscularly every 4 wk†
Penicillin V potassium	250 mg orally twice daily
Sulfadiazine	1 g orally once daily
Macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine)‡	Varies

*In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 y or until the patient is 40 y of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement.

†Administration every 3 wk is recommended in certain high-risk situations.

‡Macrolide antibiotics should not be used in persons taking other medications that inhibit cytochrome P450 3A, such as azole antifungal agents, HIV protease inhibitors, and some selective serotonin reuptake inhibitors.

Adapted from Gerber et al.¹

isolated muscle training may be used to strengthen individual muscle groups. Most patients with LV systolic dysfunction and severe VHD will undergo intervention for the valve itself. However, if intervention is declined or not feasible, standard GDMT drug therapy for LV systolic dysfunction should be continued, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone antagonists, and/or sacubitril/valsartan and biventricular pacing, as indicated in the guidelines for heart failure (HF).¹ In patients with stenotic valve lesions, abrupt lowering of blood pressure should be avoided.¹ Rheumatic fever prophylaxis and infective endocarditis (IE) prophylaxis should be provided to appropriate groups of patients, as outlined in Sections 2.4.1 and 2.4.2. The maintenance of optimal oral health remains the most important component of an overall healthcare program in preventing IE. Influenza and pneumococcal vaccinations should follow standard recommendations in patients with VHD. For subsets of patients with AF and VHD, anticoagulation is discussed in Section 2.4.3.

2.4.1. Secondary Prevention of Rheumatic Fever

Recommendation for Secondary Prevention of Rheumatic Fever		
COR	LOE	Recommendation
1	C-EO	1. In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated (Tables 6 and 7). ¹

Synopsis

Rheumatic fever is an important cause of VHD worldwide, although it is less common in high-income countries. Rapid detection and treatment of streptococcal pharyngitis constitute primary prevention of rheumatic fever. For patients with previous episodes of rheumatic fever or in those with evidence of rheumatic heart disease, long-term antistreptococcal prophylaxis is indicated for secondary prevention.¹

Table 7. Duration of Secondary Prophylaxis for Rheumatic Fever

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

*Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement.

†Clinical or echocardiographic evidence.

VHD indicates valvular heart disease.

Adapted from Gerber et al.¹

Recommendation-Specific Supportive Text

1. Recurrent rheumatic fever is associated with a worsening of rheumatic heart disease. However, infection with group A streptococcus does not have to be symptomatic to trigger a recurrence, and rheumatic fever can recur even when the symptomatic infection is treated. Prevention of recurrent rheumatic fever requires long-term antimicrobial prophylaxis rather than recognition and treatment of acute episodes of group A streptococcus pharyngitis. The recommended treatment regimens and duration of secondary prophylaxis are shown in Tables 6 and 7.

2.4.2. IE Prophylaxis

Recommendations for IE Prophylaxis		
Referenced studies that support the recommendations are summarized in Online Data Supplement 1.		
COR	LOE	Recommendations
2a	C-LD	1. Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with VHD who have any of the following ¹⁻⁹ : a. Prosthetic cardiac valves, including transcatheter-implemented prostheses and homografts. b. Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. c. Previous IE. d. Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. e. Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve.
3: No Benefit	B-NR	2. In patients with VHD who are at high risk of IE, antibiotic prophylaxis is not recommended for nondental procedures (eg, TEE, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. ^{10,11}

Synopsis

With the absence of RCTs addressing the efficacy of antibiotic prophylaxis for prevention of IE^{1,12–14} and given uncertainty about which patient populations are at highest risk, these recommendations are based on pathophysiological considerations, limited data, and clinical expertise. A prospective study demonstrated that prophylactic antibiotics given to patients for what is typically considered a high-risk dental procedure reduced but did not eliminate the incidence of bacteremia.² A 2013 Cochrane Database systematic review of antibiotic prophylaxis for the prevention of IE in dentistry concluded that there is no evidence to determine whether antibiotic prophylaxis is effective or ineffective, highlighting the need for further study of this long-standing clinical dilemma.¹ Epidemiological data conflict with regard to changes in the incidence of IE after adoption of more limited antibiotic prophylaxis guidelines.^{15–22} The consensus of the writing committee is that antibiotic prophylaxis is reasonable for the subset of patients at highest risk of developing IE and at high risk of experiencing adverse outcomes from IE. There is no evidence for IE prophylaxis in gastrointestinal procedures or genitourinary procedures, in the absence of known active infection.

Recommendation-Specific Supportive Text

1. The risk of developing IE is highest in patients with a prosthetic valve, prior IE, or congenital heart disease with residual flow disturbances.³ IE has been reported to occur after transcatheter aortic valve implantation (TAVI) at rates equal to or exceeding those associated with surgical aortic valve replacement (SAVR) and is associated with a high 1-year mortality rate of 75%.^{23,24} IE may also occur after valve repair with prosthetic material, which results in high in-hospital and 1-year mortality rates, even with surgical intervention.^{25,26} IE appears to be more common in heart transplant recipients than in the general population, according to limited data.³ The risk of IE is highest in the first 6 months after transplantation because of endothelial disruption, high-intensity immunosuppressive therapy, frequent central venous catheter access, and frequent endomyocardial biopsies.³ Persons at risk of IE can reduce potential sources of bacterial seeding by maintaining optimal oral health through regular professional dental care and the use of appropriate dental products, such as manual, powered, and ultrasonic toothbrushes; dental floss; and other plaque-removal devices.
2. Transient bacteremia is commonly seen in routine activities such as brushing teeth and flossing (20% to 68%), using toothpicks (20% to 40%), and simply chewing food (7% to 51%).

The incidence of IE after most procedures is low, with no controlled data supporting the benefit of antibiotic prophylaxis. Indiscriminate use of antibiotics can be associated with the development of resistant organisms, *Clostridium difficile* colitis, unnecessary expense, and drug toxicity. The rate of transient bacteremia during or immediately after endoscopy is 2% to 5%, and the organisms typically identified are unlikely to cause IE.^{11,27,28} The rate of bacteremia does not increase with biopsy, polypectomy, or sphincterotomy. Some gastrointestinal procedures are associated with rates of bacteremia higher than that for simple endoscopy; these procedures include esophageal dilation (as high as 45%), sclerotherapy (31%), and endoscopic retrograde cholangiopancreatography (6% to 18%).²⁹ However, no studies have shown reduced rates of IE with antibiotic prophylaxis. Surgery, instrumentation, or diagnostic procedures that involve the genitourinary tract may cause bacteremia. In the absence of infection, the rate of bacteremia after urinary tract procedures is low. In patients with bacteriuria, antimicrobial therapy before elective procedures, including lithotripsy, typically is provided.³⁰

2.4.3. Anticoagulation for AF in Patients With VHD

Recommendations for Anticoagulation for AF in Patients With VHD		
Referenced studies that support the recommendations are summarized in Online Data Supplement 2.		
COR	LOE	Recommendations
1	A	1. For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non-vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered on the basis of the patient's CHA ₂ DS ₂ -VASc score. ^{1,2}
1	C-EO	2. For patients with AF and rheumatic MS, long-term VKA oral anticoagulation is recommended.
2a	B-NR	3. For patients with new-onset AF ≤3 months after surgical or transcatheter bioprosthetic valve replacement, anticoagulation with a VKA is reasonable. ^{3–6}
3: Harm	B-R	4. In patients with mechanical heart valves with or without AF who require long-term anticoagulation with VKA to prevent valve thrombosis, NOACs are not recommended. ⁷

Synopsis

Patients with VHD and AF should be evaluated for risk of thromboembolic events and to treat them with oral anticoagulation if they are at high risk. VKAs are the anticoagulation drugs of choice for patients with rheumatic MS and mechanical heart valves. NOACs are an alternative to VKAs in patients with AF and 1) with

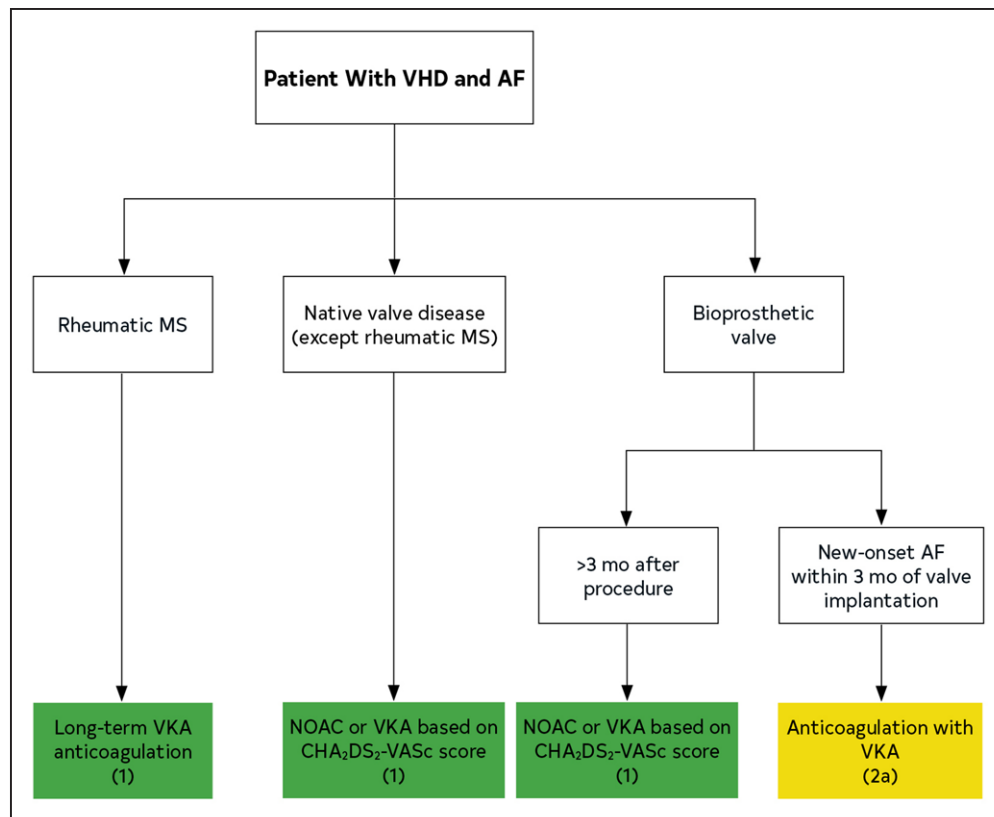


Figure 1. Anticoagulation for AF in Patients With VHD.

Colors correspond to Table 2. AF indicates atrial fibrillation; MS, mitral stenosis; NOAC, non-vitamin K oral anticoagulant; VHD, valvular heart disease; and VKA, vitamin K antagonist.

bioprosthetic valves >3 months after implantation or, 2) with native VHD excluding rheumatic MS (Figure 1).

Recommendation-Specific Supportive Text

1. The 4 large RCTs^{8–14} comparing NOACs with warfarin included small numbers of patients with VHD, prior valve repair, and bioprosthetic valves (excluding moderate to severe rheumatic MS and mechanical heart valves). In addition to the subsequent meta-analyses,^{1,15–17} examinations of insurance claims data and large registries¹⁸ have consistently confirmed no signal for a differential effect between NOAC and VKA therapy.^{19,20} More consistently observed is a net clinical benefit, with fewer events in patients using NOACs than in patients on VKA therapy. Validation of the CHA₂DS₂-VASc risk schema in patients with VHD (excluding moderate to severe rheumatic MS and mechanical heart valves) has been performed in large registries,² confirming the applicability of this score. Bioprosthetic valves do not appear to be independent predictors of thromboembolic events in patients with AF.¹⁹
2. The coexistence of AF and rheumatic MS is common and confers a substantial risk of thromboembolic events. These patients have been specifically excluded from NOAC trials, yet a single registry study and a US claims database analysis do suggest that NOACs may be potentially preferable.^{21,22} These findings need further validation, and currently the use of NOACs cannot be supported over VKA (target international normalized ratio [INR] of 2.5).
3. Postoperative AF after VHD intervention is associated with increased stroke and mortality rates^{3,4} irrespective of the CHA₂DS₂-VASc score. Anticoagulation in this setting may reduce these endpoints. There are conflicting data about the safety and efficacy of NOAC therapy in patients early after implantation of a bioprosthesis.^{5,6,23} Until more data are available, the writing committee favors using VKA for patients with AF in the first 3 months after surgical or transcatheter bioprosthetic valve implantation to prevent thromboembolic events. The optimal duration of anticoagulation is not well defined. Repeat evaluation is encouraged in all patients to detect arrhythmia recurrence in the context of their CHA₂DS₂-VASc scores.
4. The phase II study comparing dabigatran to warfarin (RE-ALIGN [Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement]) was halted prematurely because of excess stroke and

Table 8. Risk Assessment for Surgical Valve Procedures

Criteria	Low-Risk SAVR (Must Meet ALL Criteria in This Column)	Low-Risk Surgical Mitral Valve Repair for Primary MR (Must Meet ALL Criteria in This Column)	High Surgical Risk (Any 1 Criterion in This Column)	Prohibitive Surgical Risk (Any 1 Criterion in This Column)
STS-predicted risk of death*	<3% AND	<1% AND	>8% OR	Predicted risk of death or major morbidity (all-cause) >50% at 30 d OR
Frailty†	None AND	None AND	≤1 Indices (moderate to severe) OR	≥2 Indices (moderate to severe) OR
Cardiac or other major organ system compromise not to be improved postoperatively‡	None AND	None AND	1 to 2 Organ systems OR	≥3 Organ systems OR
Procedure-specific impediment§	None	None	Possible procedure-specific impediment	Severe procedure-specific impediment

*Use of the STS Predicted Risk of Mortality (<http://riskcalc.sts.org/stswebriskcalc/#/>) to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 standard deviation of the STS average observed/expected mortality ratio for the procedure in question. The EUROSCORE II risk calculator may also be considered for use and is available at <http://www.euroscore.org/calc.html>.

†Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) plus independence in ambulation (no walking aid or assistance required, or completion of a 5-m 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 include cardiac dysfunction (severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension); kidney dysfunction (chronic kidney disease, stage 3 or worse); pulmonary dysfunction (FEV₁ <50% or D_{lco2} <50% of predicted); central nervous system dysfunction (dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular accident with persistent physical limitation); gastrointestinal dysfunction (Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0); cancer (active malignancy); and liver dysfunction (any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy).

§Examples of procedure-specific impediments include presence of tracheostomy, heavily calcified (porcelain) ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, and radiation damage.

D_{lco2} indicates diffusion capacity for carbon dioxide; FEV₁, forced expiratory volume in 1 s; INR, international normalized ratio; LV, left ventricular; MR, mitral regurgitation; RV, right ventricular; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; and VKA, vitamin K antagonist.

bleeding in the dabigatran group. Until there is an explanation of why these adverse events occurred, there is insufficient evidence to support the use of NOACs for patients with mechanical heart valves.⁷

2.5. Evaluation of Surgical and Interventional Risk

Recommendation for Evaluation of Surgical and Interventional Risk		
COR	LOE	Recommendation
1	C-EO	1. For patients with VHD for whom intervention is contemplated, individual risks should be calculated for specific surgical and/or transcatheter procedures, using online tools when available, and discussed before the procedure as a part of a shared decision-making process.

Synopsis

Risk assessment has become a foundational element of the preprocedural evaluation of patients with VHD for whom intervention to correct the valve lesion may be contemplated. Although there are limitations to the scoring systems used to estimate the risk of adverse outcomes, these estimates provide a useful point of reference against which procedural benefits can be weighed. Numerical estimates of risk are just one component of the multidisciplinary team (MDT) assessment process, and factors not routinely included in risk algorithms (eg, liver disease, porcelain aorta) add important

dimensions. The availability of TAVI for treatment of symptomatic severe aortic stenosis (AS) across the surgical risk spectrum emphasizes the need to have discussions about younger age at implantation, valve durability, and the potential need for permanent pacemaker implantation. For young patients (eg, <65 years of age) who opt for a surgical bioprosthesis, strategies for sequential procedures over a longer follow-up period (ie, valve-in-valve [ViV] TAVI versus reoperation) must be addressed.

Recommendation-Specific Supportive Text

1. The decision to intervene, as well as the type of procedure recommended, is based on an assessment of patient-, procedure-, and institution- or operator-specific short-term risks and long-term benefits (Table 8). Surgical mortality rate and major morbidity risks can be calculated with a web-based tool derived from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery database for 6 specific procedures (<http://riskcalc.sts.org/stswebriskcalc/calculate>). TAVI-specific risk prediction tools are also available (<http://tools.acc.org/TAVIRisk/#!/content/evaluate/>).¹⁻⁶ Frailty assessment for at-risk patients is routine.⁷⁻¹¹ Patients toward the higher end of the risk spectrum, for whom intervention would be futile or associated with a high likelihood of a poor outcome, should

Table 9. Examples of Procedure-Specific Risk Factors for Interventions Not Incorporated Into Existing Risk Scores

SAVR	TAVI	Surgical Mitral Valve Repair or Replacement	TEER
Technical or anatomic			
Prior mediastinal radiation	Aorto-iliac occlusive disease precluding transfemoral approach	Prior sternotomy	Multivalve disease
Ascending aortic calcification (porcelain aorta may be prohibitive)	Aortic arch atherosclerosis (protuberant lesions) Severe MR or TR Low-lying coronary arteries Basal septal hypertrophy Valve morphology (eg, bicuspid or unicuspid valve) Extensive LV outflow tract calcification	Prior mediastinal radiation Ascending aortic calcification (porcelain aorta may be prohibitive)	Valve morphology (eg, thickening, perforations, clefts, calcification, and stenosis) Prior mitral valve surgery
Comorbidities			
Severe COPD or home oxygen therapy Pulmonary hypertension Severe RV dysfunction Hepatic dysfunction Frailty*	Severe COPD or home oxygen therapy Pulmonary hypertension Severe RV dysfunction Hepatic dysfunction Frailty*	Severe COPD or home oxygen therapy Pulmonary hypertension Hepatic dysfunction Frailty*	Severe COPD or home oxygen therapy Pulmonary hypertension Hepatic dysfunction Frailty*
Futility			
STS score >15 Life expectancy <1 y Poor candidate for rehabilitation	STS score >15 Life expectancy <1 y Poor candidate for rehabilitation	STS score >15 Life expectancy <1 y Poor candidate for rehabilitation	STS score >15 Life expectancy <1 y Poor candidate for rehabilitation

*Validated frailty scores include the Katz Activities of Daily Living Score.^{10,34,35}

COPD indicates chronic obstructive pulmonary disease; MR, mitral regurgitation; RV, right ventricular; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; and TR, tricuspid regurgitation.

be identified.^{12–18} Risk prediction tools for transcatheter mitral valve repair are comparatively less robust.^{17–19} The relationship between operator/institutional case volume and outcomes has been explored for surgical²⁰ and transcatheter^{21–23} aortic valve replacement (AVR), surgical mitral valve repair and replacement,^{24–32} and transcatheter mitral valve repair.³³ Table 9 includes examples of several factors that impact outcomes but are not routinely captured in currently available risk scores. Perioperative mortality rates for 6 specific surgical procedures are shown in Table 10. The potential to return to activities of daily living after an intervention must be considered.

Table 10. Median Operative Mortality Rates for Specific Surgical Procedures (STS Adult Cardiac Surgery Database, 2019)

Procedure	Mortality Rate (%)
AVR	2.2
AVR and CABG	4
AVR and mitral valve replacement	9
Mitral valve replacement	5
Mitral valve replacement and CABG	9
Mitral valve repair	1
Mitral valve repair and CABG	5

AVR indicates aortic valve replacement; CABG, coronary artery bypass graft surgery; and STS, Society of Thoracic Surgeons.

2.6. The Multidisciplinary Heart Valve Team and Heart Valve Centers

Recommendations for the Multidisciplinary Heart Valve Team and Heart Valve Centers		
COR	LOE	Recommendations
1	C-EO	1. Patients with severe VHD should be evaluated by a Multidisciplinary Heart Valve Team (MDT) when intervention is considered.
2a	C-LD	2. Consultation with or referral to a Primary or Comprehensive Heart Valve Center is reasonable when treatment options are being discussed 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. ^{1–19}

Synopsis

The value of the MDT has become increasingly apparent as options in the treatment of VHD have broadened. Heart Valve Centers, in the context of an integrated multi-institutional model of care for patients with VHD, allow optimization of patient outcomes through improved decision-making and matching of patients to providers with appropriate expertise, experience, and resources.¹² Primary and Comprehensive Heart Valve Centers are defined by their offerings and expertise in the management of patients with VHD¹² (Table 11).

Table 11. Structure of Primary and Comprehensive Valve Centers

Comprehensive (Level I) Valve Center	Primary (Level II) Valve Center
Interventional procedures*	
TAVI–transfemoral	TAVI–transfemoral
Percutaneous aortic valve balloon dilation	Percutaneous aortic valve balloon dilation
TAVI–alternative access, including transthoracic (transaortic, transapical) and extrathoracic (eg, subclavian, carotid, caval) approaches	
Valve-in-valve procedures	
TEER	
Prosthetic valve paravalvular leak closure	
Percutaneous mitral balloon commissurotomy	
Surgical procedures*	
SAVR	SAVR
Valve-sparing aortic root procedures	
Aortic root procedures for aneurysmal disease	
Concomitant septal myectomy with AVR	
Root enlargement with AVR	
Mitral repair for primary MR	Mitral repair for posterior leaflet primary MR†
Mitral valve replacement‡	Mitral valve replacement‡
Multivalve operations	
Reoperative valve surgery	
Isolated or concomitant tricuspid valve repair or replacement	Concomitant tricuspid valve repair or replacement with mitral surgery
Imaging personnel	
Echocardiographer with expertise in valve disease and transcatheter and surgical interventions	Echocardiographer with expertise in valve disease and transcatheter and surgical interventions
Expertise in CT with application to valve assessment and procedural planning	Expertise in CT with application to valve assessment and procedural planning
Interventional echocardiographer to provide imaging guidance for transcatheter and intraoperative procedures	
Expertise in cardiac MRI with application to assessment of VHD	
Criteria for imaging personnel	
A formalized role/position for a “valve echocardiographer” who performs both the pre- and postprocedural assessment of valve disease	A formalized role/position for a “valve echocardiographer” who performs both the pre- and postprocedural assessment of valve disease
A formalized role/position for the expert in CT who oversees the preprocedural assessment of patients with valve disease	A formalized role/position for the expert in CT who oversees the preprocedural assessment of patients with valve disease
A formalized role/position for an interventional echocardiographer	
Institutional facilities and infrastructure	
MDT	MDT
A formalized role/position for a dedicated valve coordinator who organizes care across the continuum and system of care	A formalized role/position for a dedicated valve coordinator who organizes care across the continuum and system of care
Cardiac anesthesia support	Cardiac anesthesia support
Palliative care team	Palliative care team
Vascular surgery support	Vascular surgery support
Neurology stroke team	Neurology stroke team
Consultative services with other cardiovascular subspecialties	
Consultative services with other medical and surgical subspecialties	
Echocardiography–3D TEE; comprehensive TTE for assessment of valve disease	Echocardiography–comprehensive TTE for assessment of valve disease
Cardiac CT	Cardiac CT
ICU	ICU

(Continued)

Table 11. Continued

Comprehensive (Level I) Valve Center	Primary (Level II) Valve Center
Temporary mechanical support (including percutaneous support devices such as intra-aortic balloon counterpulsation, temporary percutaneous ventricular assist device or ECMO)	Temporary mechanical support (including percutaneous support devices such as intra-aortic balloon counterpulsation, temporary percutaneous ventricular assist device or ECMO)
Left/right ventricular assist device capabilities (on-site or at an affiliated institution)	
Cardiac catheterization laboratory, hybrid catheterization laboratory, or hybrid OR laboratory§	Cardiac catheterization laboratory
PPM and ICD implantation	PPM and ICD implantation
Criteria for institutional facilities and infrastructure	
IAC echocardiography laboratory accreditation	IAC echocardiography laboratory accreditation
24/7 intensivist coverage for ICU	

*A primary (Level II) Center may provide additional procedures traditionally offered at a Comprehensive (Level I) Center as long as the criteria for competence and outcomes are met.

†If intraoperative imaging and surgical expertise exist.

‡If mitral valve anatomy is not suitable for valve repair.

§Equipped with a fixed radiographic imaging system and flat-panel fluoroscopy, offering catheterization laboratory-quality imaging and hemodynamic capability.

AVR indicates aortic valve replacement; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ICD, implantable cardioverter defibrillator; IAC, Intersocietal Accreditation Commission; ICU, intensive care unit; MDT, multidisciplinary team; MR, mitral regurgitation; MRI, magnetic resonance imaging; OR operating room; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; TEER, transcatheter edge-to-edge repair; TTE, transthoracic echocardiography; VHD, valvular heart disease; and ViV, valve-in-valve.

Used with permission from Nishimura et al.¹²

Recommendation-Specific Supportive Text

1. The MDT is an established feature of heart valve programs²⁰ and has been formally endorsed by the ACC, the American Society of Echocardiography, the Society for Cardiovascular Angiography and Interventions, the American Association for Thoracic Surgery, and the STS.¹² Key members of the MDT include cardiologists with subspecialty expertise in the clinical evaluation of patients with VHD, as well as specialists in advanced cardiovascular imaging. For the evaluation of the patient with secondary mitral regurgitation (MR) and tricuspid regurgitation (TR), a specialist in HF also is included. Interventional cardiologists with training and expertise in VHD and surgeons experienced in the treatment of VHD anchor the MDT. Other team members include cardiovascular nurses, cardiovascular anesthesiologists, and intensivists involved in periprocedural care. Finally, the engagement of the primary clinical cardiologist and patient is of critical importance. The MDT facilitates presentation of all appropriate options for medical, interventional, and surgical treatment to the patient in a balanced manner, using tools and techniques for shared decision-making in which patient preferences are considered.
2. Decision-making is particularly challenging for the asymptomatic VHD patient, for whom the risks of operative mortality and perioperative morbidity must be very low and the chances of a successful and durable surgical outcome very high. There is a substantial body of literature to

support a relationship between institutional volume and mortality rate for many cardiovascular procedures, including SAVR,^{1–5} TAVI,⁶ and surgical mitral valve repair.^{7–11} Consideration should be given to consultation with or referral to a Primary or Comprehensive Heart Valve Center for asymptomatic patients with severe VHD. Although excellent outcomes certainly can be achieved at lower-volume centers, assurance of outcomes equivalent to those of a higher-volume center is statistically more challenging.¹² Similarly, for patients with multiple comorbidities for whom multispecialty collaboration is anticipated, care at a Comprehensive or Primary Valve Center ensures optimal outcomes. Although findings are mixed,¹³ there are data to support relationships between center volume and complication rates in cardiac surgical care,¹⁴ between center volume and failure to rescue after procedural complications,^{15–17} and between center volume and elements of infrastructure support.^{18,19}

2.7. Management of Patients With VHD After Valve Intervention

Interventions in patients with VHD include both transcatheter and surgical approaches. A valve intervention leaves the patient with either a prosthetic valve or a valve repair, often with an implanted device or other prosthetic material. Valve intervention does not eliminate valve disease; it replaces native valve disease with palliated valve disease. Patients with VHD continue to require periodic evaluation after intervention

for early postprocedural issues, long-term medical therapy, monitoring of the prosthetic valve or repair, management of concurrent cardiac conditions, and persistent symptoms or functional limitation. Endocarditis prophylaxis is discussed in Section 2.4.2; antithrombotic therapy for prosthetic valves in Sections 11.2 to 11.5; and prosthetic valve complications, including valve thrombosis, stenosis, or regurgitation, in Sections 11.6 to 11.8.

2.7.1. Procedural Complications

The most common complication early after surgical valve replacement is postoperative AF, which occurs in up to one-third of patients within 3 months of surgery (see Sections 2.4.3 and 14.1). Other complications include stroke, vascular and bleeding complications, pericarditis, heart block requiring temporary or permanent pacing (especially after AVR), HF, renal dysfunction, and infection. Complications after transcatheter interventions depend on the specific procedure but can include the need for permanent pacing, paravalvular leak, stroke, vascular complications, and residual valve dysfunction.

2.7.2. Primary and Secondary Risk Factor Evaluation and Treatment

Concurrent coronary artery disease (CAD) is common in adults with VHD. Management of CAD at the time of valve intervention is discussed in Section 14.2. After valve intervention, evaluate and treat patients with CAD risk factors according to current guidelines for primary and secondary prevention. Although there is no convincing evidence that treating CAD risk factors will reduce the likelihood of progressive valve dysfunction after intervention, cardiovascular outcomes are improved overall because of a reduced rate of coronary events.

2.7.3. Persistent Symptoms After Valve Intervention

Persistent symptoms occur in many patients after valve intervention. The first step in evaluation is to assess valve function to ensure symptoms are not caused by persistent or recurrent stenosis, regurgitation, or a valve complication. The next step is to evaluate and treat any concurrent cardiac disease and noncardiac conditions that may be the cause of symptoms. Symptoms also may be attributable to irreversible consequences of valve disease, including LV systolic and diastolic dysfunction, pulmonary hypertension, and RV dysfunction. Treatment of symptoms for these patients is based on GDMT for HF and/or pulmonary hypertension.

2.7.4. Periodic Imaging After Valve Intervention

Recommendation for Periodic Imaging After Valve Intervention		
COR	LOE	Recommendation
1	C-EO	1. In asymptomatic patients with any type of valve intervention, a baseline postprocedural TTE followed by periodic monitoring with TTE is recommended, depending on type of intervention, length of time after intervention, ventricular function, and concurrent cardiac conditions.

Synopsis

A TTE is useful after either catheter-based or surgical intervention to provide a baseline measurement of valve function and the status of the ventricle. Repeat TTE is recommended with either new symptoms or a change in the physical examination. The timing of periodic follow-up imaging is based on the type of valve intervention.

Table 12. Timing of Periodic Imaging After Valve Intervention

Valve Intervention	Imaging Follow-Up*	
	Minimal Imaging Frequency†	Location
Mechanical valve (surgical)	Baseline	Primary Valve Center
Bioprosthetic valve (surgical)	Baseline, 5 and 10 y after surgery,‡ and then annually	Primary Valve Center
Bioprosthetic valve (transcatheter)	Baseline and then annually	Primary Valve Center
Mitral valve repair (surgical)	Baseline, 1 y, and then every 2 to 3 y	Primary Valve Center
Mitral valve repair (transcatheter)	Baseline and then annually	Comprehensive Valve Center
Bicuspid aortic valve disease	Continued post-AVR monitoring of aortic size if aortic diameter is ≥ 4.0 cm at time of AVR, as detailed in Section 5.1	Primary Valve Center

*Initial postprocedural TTE is recommended for all patients, ideally 1 to 3 months after the procedure. Annual clinical follow-up is recommended annually for all patients after valve intervention at a Primary or Comprehensive Valve Center.

†Repeat imaging is appropriate at shorter follow-up intervals for changing signs or symptoms, during pregnancy, and to monitor residual or concurrent cardiac dysfunction.

‡Imaging may be done more frequently in patients with bioprosthetic surgical valves if there are risk factors for early valve degeneration (eg, younger age, renal failure, diabetes).

AVR indicates aortic valve replacement; and TTE, transthoracic echocardiography.

Recommendation-Specific Supportive Text

1. In patients who have had a valve intervention, most cardiologists continue to see patients for a clinical history and physical examination at annual intervals, or more frequently if needed for symptoms or concurrent conditions. A baseline TTE study is recommended after all valve interventions, including replacement with a prosthetic valve (see Section 11.1). This baseline postprocedural study ideally is performed 1 to 3 months after intervention to ensure loading conditions have returned to normal, but in some cases it may need to be done during the index hospitalization for the patient's convenience. The timing of subsequent periodic imaging after valve intervention is based on the type of valve prosthesis or repair, length of time after valve intervention, residual valve dysfunction, ventricular size and systolic function, and any concurrent cardiac conditions (Table 12). TTE is the standard approach for periodic imaging, supplemented by TEE when prosthetic mitral valve dysfunction is a concern (see Section 11.1). Additional imaging with CT, fluoroscopy CMR, or PET is reserved for patients for whom there is concern about valve dysfunction (see Section 11.1) or endocarditis (see Section 12.1).^{1,2}

3. AORTIC STENOSIS

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 13 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 stage is defined by patient symptoms, valve anatomy, valve hemodynamics, and changes in the LV and vasculature. Hemodynamic severity is best characterized by the transaortic maximum velocity (or mean pressure gradient) when the transaortic volume flow rate is normal. Some patients with AS have a low transaortic volume flow rate that is either because of LV systolic dysfunction with a low LVEF or because of a small, hypertrophied LV with a low stroke volume. Severe AS with low flow is designated D2 (with a low LVEF) or D3 (with a normal LVEF). Meticulous attention to detail is required during assessment of 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.

3.2. Aortic Stenosis

3.2.1. Diagnosis and Follow-Up

3.2.1.1. Diagnostic Testing: Initial Diagnosis

Recommendations for Diagnostic Testing: Initial Diagnosis of AS
Referenced studies that support the recommendations are summarized in Online Data Supplement 3.

COR	LOE	Recommendations
1	A	1. In patients with signs or symptoms of AS or a BAV, TTE is indicated for accurate diagnosis of the cause of AS, assessment of hemodynamic severity, measurement of LV size and systolic function, and determination of prognosis and timing of valve intervention. ^{1,2}
1	B-NR	2. In patients with suspected low-flow, low-gradient severe AS with normal LVEF (Stage D3), optimization of blood pressure control is recommended before measurement of AS severity by TTE, TEE, cardiac catheterization, or CMR. ³⁻⁷
2a	B-NR	3. In patients with suspected low-flow, low-gradient severe AS with reduced LVEF (Stage D2), low-dose dobutamine stress testing with echocardiographic or invasive hemodynamic measurements is reasonable to further define severity and assess contractile reserve. ⁸⁻¹⁰
2a	B-NR	4. In patients with suspected low-flow, low-gradient severe AS with normal or reduced LVEF (Stages D2 and D3), calculation of the ratio of the outflow tract to aortic velocity is reasonable to further define severity. ^{1,11-13}
2a	B-NR	5. In patients with suspected low-flow, low-gradient severe AS with normal or reduced LVEF (Stages D2 and D3), measurement of aortic valve calcium score by CT imaging is reasonable to further define severity. ¹⁴⁻¹⁸

Synopsis

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.

Recommendation-Specific Supportive Text

1. In adult patients, physical examination may not be accurate for diagnosis of and assessment of severity of AS. Echocardiographic imaging allows reliable evaluation of valve anatomy and motion and the degree of valve obstruction. In addition, TTE is useful for measuring LV size and systolic function, identifying concurrent AR or MR, and estimating pulmonary systolic pressure.^{1,2,11,12,19-27}
2. Measurements of AS severity made when the patient is hypertensive may underestimate or, less often, overestimate stenosis severity. Systemic hypertension imposes a second pressure load on the LV, in addition to valve obstruction, which

Table 13. Stages of AS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	BAV (or other congenital valve anomaly) Aortic valve sclerosis	Aortic $V_{max} < 2$ m/s with normal leaflet motion	None	None
B	Progressive AS	Mild to moderate leaflet calcification/fibrosis 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 ΔP 20–39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	Severe leaflet calcification/fibrosis 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 ≤ 1.0 cm ² (or AVAi 0.6 cm ² /m ²) but not required to define severe AS Very severe AS is an aortic $V_{max} \geq 5$ m/s or mean $P \geq 60$ mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV systolic dysfunction	Severe leaflet calcification/fibrosis 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 ≤ 1.0 cm ² (or AVAi 0.6 cm ² /m ²) but not required to define severe AS	LVEF $< 50\%$	None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification/fibrosis 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 ≤ 1.0 cm ² (or AVAi ≤ 0.6 cm ² /m ²) but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea, decreased exercise tolerance, or HF Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA ≤ 1.0 cm ² with resting aortic $V_{max} < 4$ m/s or mean $\Delta P < 40$ mm Hg Dobutamine stress echocardiography shows AVA < 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 with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA ≤ 1.0 cm ² (indexed AVA ≤ 0.6 cm ² /m ²) with an aortic $V_{max} < 4$ m/s or mean $\Delta P < 40$ mm Hg AND Stroke volume index < 35 mL/m ² Measured when patient is normotensive (systolic blood pressure < 140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF $\geq 50\%$	HF Angina Syncope or presyncope

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

results in a lower forward stroke volume and lower transaortic pressure gradient than when the patient is normotensive. Thus, Doppler velocity data and invasive pressure measurements ideally are recorded when the patient is normotensive. If results indicate only moderate stenosis but were recorded when the patient was hypertensive, repeat measurements when the blood

pressure is better controlled ensure that a diagnosis of severe AS is not missed.

- Patients with severe AS and LVEF $< 50\%$ present with an aortic valve area < 1.0 cm² but a low transvalvular velocity and pressure gradient (ie, velocity < 4 m/s or mean gradient < 40 mm Hg) at rest. In these patients, severe AS with LV systolic dysfunction attributable to afterload

mismatch must be distinguished from primary myocardial dysfunction with only moderate AS. Dobutamine stress echocardiography may be useful with measurement of aortic velocity (or mean pressure gradient) and valve area at baseline and at higher flow rates (maximum dose dobutamine 20 mcg/kg per minute) under appropriate clinical and hemodynamic monitoring. Severe AS is characterized by a fixed valve area, resulting in an increase in transaortic velocity to ≥ 4 m/s (mean gradient ≥ 40 mm Hg) at any flow rate, but with valve area remaining ≤ 1.0 cm². In contrast, in patients with moderate AS and primary LV dysfunction, there is an increase in valve area as volume flow rate increases, resulting in only a modest increase in transaortic velocity or gradient. Some patients fail to show an increase in stroke volume $\geq 20\%$ with dobutamine, referred to as “lack of contractile reserve” or “lack of flow reserve.”^{8,9,19,28–32}

4. The key measurements for clinical decision-making in patients with AS are the maximum aortic velocity, mean pressure gradient (calculated with the Bernoulli equation), and valve area (calculated with the continuity equation). An additional measurement that may be useful when there are discrepancies in these measures or in other clinical or imaging data is the ratio of the velocity in the LV outflow tract proximal to the aortic valve and the velocity in the narrowed aortic orifice. The outflow tract-to-aortic velocity ratio is independent of body size and eliminates potential errors in calculated valve area related to measurement of LV outflow tract diameter or area. A normal ratio is close to 1.0, whereas a ratio of ≤ 0.25 corresponds to a valve area 25% of normal for that patient, which is consistent with severe AS and is a predictor of symptom onset and adverse outcomes.^{12,13,21,22,23}
5. The degree of aortic valve calcification is a strong predictor of clinical outcome, even when evaluated qualitatively by echocardiography.³³ Quantitation of aortic valve calcium by CT imaging is especially useful in patients with low-flow, low-gradient AS of unclear severity with either a normal or reduced LVEF. Sex-specific Agaston unit thresholds for diagnosis of severe AS are 1300 in women and 2000 in men. These different thresholds reflect the contribution of leaflet fibrosis, in addition to calcification, to increased leaflet stiffness in women. CT imaging also is used for procedural planning in patients undergoing TAVI, for measurement of annulus area,

leaflet length, and the annular-to-coronary ostial distance.^{14–18}

3.2.1.2. Diagnostic Testing: Changing Signs or Symptoms

In patients with known valvular AS, repeat TTE is prudent when physical examination shows an increase in the loudness of the murmur, the murmur peaks later in systole, the A2 component of the second heart sound is diminished or absent, or symptoms occur that might be attributable to AS. Repeat TTE is also appropriate in patients with AS who are exposed to increased hemodynamic demands, either electively, such as with non-cardiac surgery or pregnancy, or acutely, such as with a systemic infection, anemia, or gastrointestinal bleeding. In these clinical settings, knowledge of the severity of valve obstruction and LV function is critical for optimizing loading conditions and maintaining a normal cardiac output.

3.2.1.3. Diagnostic Testing: Routine Follow-Up

Timing of periodic clinical evaluation of asymptomatic patients with severe AS depends on comorbidities and patient-specific factors, as well as AS severity (Table 4). When severe AS is present (aortic velocity ≥ 4.0 m/s), the rate of progression to symptoms is high, with an event-free survival rate of only 30% to 50% at 2 years. In patients with asymptomatic severe AS, periodic monitoring is needed because symptom onset is insidious and may not be recognized by the patient. With moderate AS (aortic velocity 3.0–3.9 m/s), the average annual rate of progression is an increase in velocity of 0.3 m/s, increase in mean pressure gradient of 7 mm Hg, and decrease in valve area of 0.1 cm². There is marked individual variability, with more rapid progression in older patients and in patients with more severe leaflet calcification. In patients with aortic sclerosis, defined as focal areas of valve calcification and leaflet thickening with an aortic velocity < 2.0 m/s, progression to severe AS occurs in about 10% of patients within 5 years. Patients with BAV disease are also at risk of progressive valve stenosis, with AS being the most common reason for intervention in patients with a BAV (Section 5.1.1).^{1–13}

3.2.1.4. Diagnostic Testing: Cardiac Catheterization

Diagnostic TTE and Doppler data can be obtained in nearly all patients, but severity of AS may be underestimated if image quality is poor or if a parallel intercept angle is not obtained between the ultrasound beam and aortic jet. When data from noninvasive testing are non-diagnostic or if there is a discrepancy between clinical and echocardiographic evaluation, cardiac catheterization for determination of severity of AS can be helpful. Transaortic pressure gradient recordings allow measurement of the mean transaortic gradient via simultaneous LV and aortic pressure measurements. Aortic valve area

is calculated with the Gorlin formula by using a Fick or thermodilution cardiac output measurement. See Section 14.1 for recommendations on coronary angiography in patients with AS.^{1,2}

3.2.1.5. Diagnostic Testing: Exercise Testing

Recommendations for Diagnostic Testing: Exercise Testing in Patients With AS		
Referenced studies that support the recommendations are summarized in Online Data Supplement 4.		
COR	LOE	Recommendations
2a	B-NR	1. In asymptomatic patients with severe AS (Stage C1), exercise testing is reasonable to assess physiological changes with exercise and to confirm the absence of symptoms. ¹⁻⁴
3: Harm	B-NR	2. In symptomatic patients with severe AS (Stage D1, aortic velocity ≥ 4.0 m/s or mean pressure gradient ≥ 40 mmHg), exercise testing should not be performed because of the risk of severe hemodynamic compromise. ⁵

Synopsis

In a subset of asymptomatic patients with severe AS, exercise testing can provide additional diagnostic and prognostic information, but it should not be performed in symptomatic patients with severe AS.

Recommendation-Specific Supportive Text

- When performed under the direct supervision of an experienced clinician, with close monitoring of blood pressure and ECG, exercise testing in asymptomatic patients is relatively safe and may provide information that is not evident during the initial clinical evaluation, particularly when the patient's functional capacity is unclear. Patients with symptoms provoked by exercise testing should be considered symptomatic, even if the clinical history is equivocal. Although it can be challenging to separate normal exercise limitations from abnormal symptoms that are attributable to AS, particularly in elderly sedentary patients, exercise-induced angina, excessive dyspnea early in exercise, dizziness, and syncope are consistent with symptoms of AS. Exercise testing can also identify a limited exercise capacity or an abnormal blood pressure response. Recording aortic valve hemodynamics with exercise is of limited value and does not show additive value for predicting clinical outcome when baseline measures of hemodynamic severity and functional status are considered. In addition, recording hemodynamics with exercise is challenging, and simpler parameters are adequate in most patients.^{2-4,6-11}

- As reported in several prospective and retrospective studies, the risk of exercise testing is low in asymptomatic patients with AS. However, exercise testing is avoided in symptomatic patients with AS because of a high risk of complications, including syncope, ventricular tachycardia, and death. In a prospective survey of 20 medical centers in Sweden that included 50 000 exercise tests done over an 18-month period, the complication rate was 18.4 per 10 000 tests; morbidity rate, 5.2 per 10 000 tests; and mortality rate, 0.4 per 10 000 tests. Although the number of patients with AS was not reported, 12 of the 92 complications occurred in patients with AS: 8 had a decline in blood pressure during exercise, 1 had asystole, and 3 had ventricular tachycardia.^{2,4,5,7-10,12}

3.2.2. Medical Therapy

Recommendations for Medical Therapy of AS		
Referenced studies that support the recommendations are summarized in Online Data Supplement 5.		
COR	LOE	Recommendations
1	B-NR	1. In patients at risk of developing AS (Stage A) and in patients with asymptomatic AS (Stages B and C), hypertension should be treated according to standard GDMT, started at a low dose, and gradually titrated upward as needed, with appropriate clinical monitoring. ¹⁻³
1	A	2. In all patients with calcific AS, statin therapy is indicated for primary and secondary prevention of atherosclerosis on the basis of standard risk scores. ⁴⁻⁶
2b	B-NR	3. In patients who have undergone TAVI, renin-angiotensin system blocker therapy (ACE inhibitor or ARB) may be considered to reduce the long-term risk of all-cause mortality. ^{7,8}
3: No Benefit	A	4. In patients with calcific AS (Stages B and C), statin therapy is not indicated for prevention of hemodynamic progression of AS. ⁴⁻⁶

Synopsis

Medical treatment of hypertension and hyperlipidemia according to GDMT is appropriate for patients with AS. ACE inhibitor or ARB treatment may reduce the mortality rate in patients with AS who underwent TAVI.

Recommendation-Specific Supportive Text

- Hypertension is common in patients with AS, may be a risk factor for AS, and adds to the total pressure overload on the LV in combination with valve obstruction. Concern that antihypertensive medications might result in a decrease in cardiac output has not been corroborated in studies of medical therapy, including 2 small RCTs, likely because AS does not result in "fixed" valve obstruction until late in the disease process. In 1616 patients

with asymptomatic AS in the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study, hypertension (n=1340) was associated with a 56% higher rate of ischemic cardiovascular events and a 2-fold higher mortality rate (both $P<0.01$) than those seen in normotensive patients with AS, although no impact on progression of valve stenosis leading to symptoms requiring AVR was seen. Medical therapy for hypertension follows standard guidelines, starting at a low dose and gradually titrating upward as needed to achieve blood pressure control. There are no studies addressing specific anti-hypertensive medications in patients with AS, but diuretics may reduce stroke volume, particularly if the LV chamber is small at baseline. In theory, ACE inhibitors may be advantageous because of the potential beneficial effects on LV fibrosis, in addition to control of hypertension. Consideration should be given to a higher target blood pressure for patients with AS than is recommended for the general population, but this is an underexplored area, and further data are needed before a different target blood pressure can be recommended for patients with AS.^{1-3,9-13}

2. Concurrent CAD is common in patients with AS, and all patients should be screened and treated for hypercholesterolemia, with GDMT used for primary and secondary prevention of CAD. In RCTs of statin therapy for mild to moderate AS, although aortic valve event rates were not reduced, the rate of ischemic events was reduced by about 20% in the statin therapy group even though these patients did not meet standard criteria for statin therapy.^{4-6,14,15}
3. In patients undergoing TAVI, observational and registry data show that those who were treated with renin-angiotensin system blocker therapy after the procedure had a lower 1-year mortality rate than those not treated with renin-angiotensin system blocker therapy, with a relative risk reduction of about 20% to 50% and an absolute risk reduction between 2.4% and 5.0%. When stratified by LVEF, having a prescription for a renin-angiotensin system inhibitor, versus no prescription, was associated with a lower 1-year mortality rate among patients with preserved LVEF but not among those with reduced LVEF.^{7,8,16,17}
4. Despite experimental models and retrospective clinical studies suggesting that lipid-lowering therapy with a statin might prevent disease progression of calcific AS, 3 large well-designed RCTs failed to show a benefit, either in terms of changes in hemodynamic severity or in clinical outcomes, in patients with mild to moderate valve obstruction. Thus, at the time of publication, there are no

data to support the use of statins for prevention of progression of AS.^{7,8,16,17}

3.2.3. Timing of Intervention

Recommendations for Timing of Intervention of AS		
Referenced studies that support the recommendations are summarized in Online Data Supplements 4 and 6 to 10.		
COR	LOE	Recommendations
1	A	1. In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated. ¹⁻⁷
1	B-NR	2. In asymptomatic patients with severe AS and an LVEF <50% (Stage C2), AVR is indicated. ⁸⁻¹¹
1	B-NR	3. In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated. ¹²⁻¹⁶
1	B-NR	4. In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (Stage D2), AVR is recommended. ¹⁷⁻²⁴
1	B-NR	5. In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (Stage D3), AVR is recommended if AS is the most likely cause of symptoms. ²⁵⁻²⁷
2a	B-NR	6. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥ 10 mmHg from baseline to peak exercise. ^{13,28-30}
2a	B-R	7. In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥ 5 m/s) and low surgical risk, AVR is reasonable. ^{15,31-35}
2a	B-NR	8. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide (BNP) level is >3 times normal. ^{32,36-38}
2a	B-NR	9. In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥ 0.3 m/s per year. ^{39,40}
2b	B-NR	10. In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in LVEF on at least 3 serial imaging studies to $<60\%$, AVR may be considered. ^{8-11,33}
2b	C-EO	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

Synopsis

See the table of recommendations for a summary of recommendations from this section and Figure 2 for indications for AVR in patients with AS. These recommendations for timing of intervention for AS apply to both SAVR and TAVI. The integrative approach to assessing risk of SAVR or TAVI is discussed in Section 2.5. The specific type of intervention for AS is discussed in Section 3.2.4.

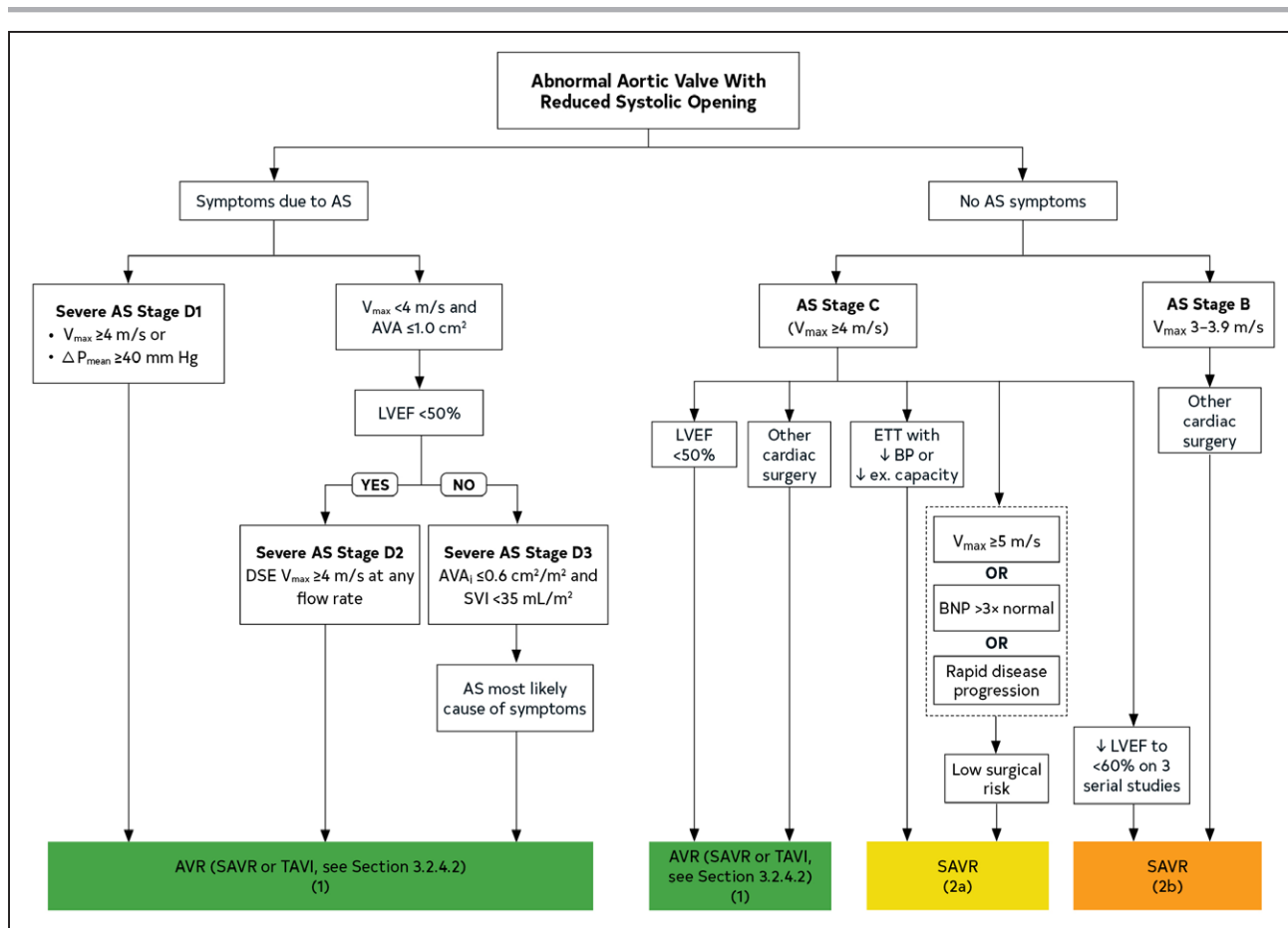


Figure 2. Timing of intervention for AS.

Colors correspond to Table 2. 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 (Stage C) and symptomatic (Stage D) AS and those with low-gradient AS (Stage D2 or D3) who do not meet the criteria for intervention. See Section 3.2.4 for choice of valve type (mechanical versus bioprosthetic [TAVI or SAVR]) when AVR is indicated. AS indicates aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean} , mean systolic pressure gradient between LV and aorta; SAVR, surgical aortic valve replacement; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; and V_{max} , maximum velocity.

Recommendation-Specific Supportive Text

1. In symptomatic patients with severe high-gradient AS (Stage D1), ample evidence demonstrates the beneficial effects of AVR on survival, symptoms, and LV systolic function.^{35,41–46} The most common initial symptom of AS is exertional dyspnea or decreased exercise tolerance. Clinical vigilance is needed to recognize these early symptoms and proceed promptly to AVR. More severe “classical” symptoms of AS, including HF, syncope, or angina, can be avoided by appropriate treatment at the onset of even mild symptoms. Outcomes after surgical or transcatheter AVR are excellent in patients who do not have a high procedural risk.^{41,43–45} Surgical series demonstrate improved symptoms after AVR, and most patients have an improvement in exercise tolerance, as documented in studies with pre- and post-AVR exercise stress testing.^{41,43–46} Historical

observation studies on outcomes in symptomatic patients with severe AS have been confirmed in RCTs comparing TAVI with palliative care in patients with a prohibitive surgical risk. The choice of surgical versus transcatheter AVR for patients with an indication for AVR is discussed in Section 3.2.4.^{1–3,5,6,12–16,35,42,47–55}

2. In asymptomatic patients with severe AS and normal LV systolic function, the survival rate during the asymptomatic phase is similar to that of age-matched controls, with a low risk of sudden death (<1% per year) when patients are followed prospectively and when patients promptly report symptom onset. However, in patients with a low LVEF and severe AS, survival is better in those who undergo AVR than in those treated medically. The depressed LVEF in many patients is caused by excessive afterload (afterload mismatch), and LV function improves after AVR in such patients. If LV dysfunction is not caused

- by afterload mismatch, survival is still improved, likely because of the reduced afterload with AVR, but improvement in LV function and resolution of symptoms might not be complete after AVR.^{17,23,24,56–62}
3. Prospective clinical studies demonstrate that disease progression occurs in nearly all patients with severe asymptomatic AS. Symptom onset within 2 to 5 years is likely when aortic velocity is ≥ 4.0 m/s or mean pressure gradient is ≥ 40 mm Hg. The additive risk of AVR at the time of other cardiac surgery is less than the risk of reoperation within 5 years.^{12–16,63–65}
 4. Mean pressure gradient is a strong predictor of outcome after AVR, with better outcomes seen in patients with higher gradients. Outcomes are poor with severe low-gradient AS but are still better with AVR than with medical therapy in those with a low LVEF, particularly when contractile reserve is present. The document “Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice” defines severe AS on dobutamine stress testing as a maximum velocity >4.0 m/s with a valve area ≤ 1.0 cm² at any point during the test protocol, with a maximum dobutamine dose of 20 mcg/kg per minute.⁶⁶ The recommendation for AVR in these patients is based on outcome data in several prospective nonrandomized studies. LVEF typically increases by 10 LVEF units and may return to normal if afterload mismatch was the cause of LV systolic dysfunction. If dobutamine stress testing indicates moderate, not severe AS, GDMT for HF can be continued without AVR. Patients without contractile reserve may also benefit from AVR, but decisions in these high-risk patients must be individualized because outcomes are poor with either surgical or medical therapy. The role of TAVI in these patients is currently under investigation.^{17,22–24,59,60,67}
 5. A subset of patients with severe AS presents with symptoms and with a low velocity, low gradient, and low stroke volume index, despite a normal LVEF. Low-flow, low-gradient severe AS with preserved LVEF should be considered in patients with a severely calcified aortic valve, an aortic velocity <4.0 m/s (mean pressure gradient <40 mm Hg), and a valve area ≤ 1.0 cm² when stroke volume index is <35 mL/m². Typically, the LV is small, with thick walls, diastolic dysfunction, and a normal LVEF ($\geq 50\%$). The first diagnostic step is to ensure that data were recorded and measured correctly. If hypertension is present, blood pressure is controlled before reevaluation of AS severity. Next, valve area is indexed to body size because an apparent small valve area may be only moderate AS in a small patient; an aortic valve area index ≤ 0.6 cm²/m² suggests severe AS. Transaortic stroke volume is calculated by Doppler or 2D imaging. Measurement of a CT calcium score often is helpful. Evaluation for other potential causes of symptoms ensures that symptoms are most likely attributable to valve obstruction. Although the survival rate after TAVI is lower in patients with low-flow severe AS than in patients with normal-flow severe AS, AVR appears beneficial, with an increase in stroke volume and improved survival as compared with medical therapy.^{18,25–27,54,68–76}
 6. Exercise testing may be helpful in clarifying symptom status in patients with severe AS. When symptoms are provoked by exercise testing, the patient is considered symptomatic and meets a COR 1 recommendation for AVR; symptoms are symptoms, whether reported spontaneously by the patient or provoked on exercise testing. The rate of symptom onset within 1 to 2 years is high (about 60% to 80%) in patients without overt symptoms who demonstrate 1) a fall of ≥ 10 mm Hg in systolic blood pressure from baseline to peak exercise or 2) a significant decrease in exercise tolerance as compared with age and sex normal standards. Management of patients with a lack of appropriate rise in BP with exercise is less clear. Decisions about elective AVR in these patients include consideration of surgical risk, patient preferences, and clinical factors, such as age and comorbid conditions.^{13,28,77–82}
 7. In patients with very severe AS and an aortic velocity ≥ 5.0 m/s or mean pressure gradient ≥ 60 mm Hg, the rate of symptom onset is approximately 50% at 2 years. On multivariable analysis of a large cohort of adults with asymptomatic AS (>500 patients), an aortic velocity ≥ 5 m/s was associated with a >6 -fold increased risk of cardiovascular mortality (hazard ratio [HR]: 6.31; 95% CI: 2.61–15.9).³³ A randomized trial of SAVR versus continued surveillance showed a significant survival benefit to early surgery in patients with aortic velocity ≥ 4.5 m/s.³¹ In patients with very severe asymptomatic AS and low surgical risk, a decision to proceed with AVR or continue watchful waiting takes into account patient age, avoidance of patient–prosthesis mismatch, anticoagulation issues, and patient preferences.^{31–33,39}
 8. An elevated serum BNP level is a marker of subclinical HF and LV decompensation. In a cohort of 387 asymptomatic adults with severe AS, elevated BNP levels were associated with an increased 5-year risk of AS-related events, with a

hazard ratio for a BNP level >300 pg/mL (3 times normal) of 7.38 (CI: 3.21 to 16.9).³² Serum BNP levels also are predictive of symptom onset during follow-up and persistent symptoms after AVR.³⁶

9. Hemodynamic progression eventually leading to symptom onset occurs in nearly all asymptomatic patients with AS once the aortic velocity reaches ≥ 2 m/s. Although the average rate of hemodynamic progression for calcific stenosis of a trileaflet valve is an increase in aortic velocity of about 0.3 m/s per year, an increase in mean gradient of 7 to 8 mmHg per year, and a decrease in valve area of 0.15 cm² per year, there is marked variability between patients in disease progression. Predictors of rapid disease progression include older age, more severe valve calcification, and a faster rate of hemodynamic progression on serial studies. In patients with an aortic velocity >4 m/s in addition to predictors of rapid disease progression, symptom onset is likely in the near future, so there is less benefit to waiting for symptom onset. Thus, elective AVR may be considered if the surgical risk is low and after consideration of other clinical factors and patient preferences.
10. In adults with initially asymptomatic severe AS, the rate of sudden death is low (<1% per year). However, an aortic velocity ≥ 5 m/s or an LVEF <60% each is associated with higher all-cause and cardiovascular mortality rates in the absence of AVR.³¹ A multivariate analysis of predictors of death in a large cohort (>500 patients) showed a >4-fold higher risk of cardiovascular death for those with an LVEF <60% than for those with a higher LVEF (HR: 4.47; 95% CI: 2.06 to 9.70).³³ A progressive decrease in LVEF is most likely in those with an LVEF <60% before AS becomes severe.^{8,9,11} Evaluation for other causes of a decline in LVEF is appropriate, particularly when AS is not yet severe, but a progressive decline in LV systolic function is of concern and should prompt more frequent evaluation; and consideration of AVR when repeat studies show a progressive decline in LVEF without other cause with a lack of response to medical therapy. The presence of at least 3 serial imaging studies showing a consistent decline in LVEF ensures that the changes seen are not simply attributable to recording, measurement, or physiological variability.^{8–11}
11. Hemodynamic progression eventually leading to symptom onset occurs in nearly all asymptomatic patients with AS. The survival rate during the asymptomatic phase is similar to age-matched controls, with a low risk of sudden death (<1% per year) when patients are followed prospectively and when patients promptly report symptom onset. The rate of symptom onset is strongly

dependent on the severity of AS, with an event-free survival rate of about 75% to 80% at 2 years in those with a jet velocity <3.0 m/s, compared with only 30% to 50% in those with a jet velocity ≥ 4.0 m/s. Patients with asymptomatic AS require periodic monitoring for development of symptoms and progressive disease (Section 3.1). In patients with moderate calcific AS undergoing cardiac surgery for other indications, the risk of progressive VHD is balanced against the risk of repeat surgery or TAVI (Sections 4.3.3 and 10). This decision must be individualized on the basis of the specific operative risk in each patient, clinical factors such as age and comorbid conditions, valve durability, and patient preferences.^{13,49,62–64}

3.2.4. Choice of Intervention

3.2.4.1. Choice of Mechanical Versus Bioprosthetic AVR

Recommendations for Choice of Mechanical Versus Bioprosthetic AVR
Referenced studies that support the recommendations are summarized in Online Data Supplements 11 and 12.

COR	LOE	Recommendations
1	C-EO	1. In patients with an indication for AVR, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and risks of anticoagulant therapy and the potential need for and risks associated with valve reintervention.
1	C-EO	2. For patients of any age requiring AVR for whom VKA anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic AVR is recommended.
2a	B-R	3. For patients <50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve. ¹
2a	B-NR	4. For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR with consideration of individual patient factors and after informed shared decision-making. ^{1–10}
2a	B-R	5. In patients >65 years of age who require AVR, it is reasonable to choose a bioprosthesis over a mechanical valve. ¹
2b	B-NR	6. In patients <50 years of age who prefer a bioprosthetic AVR and have appropriate anatomy, replacement of the aortic valve by a pulmonic autograft (the Ross procedure) may be considered at a Comprehensive Valve Center. ^{11–13}

Synopsis

Shared decision-making about the choice of prosthetic valve type is influenced by several factors,

including patient age, values, and preferences; expected bioprosthetic valve durability, avoidance of patient–prosthesis mismatch, and the potential need for and timing of reintervention; and the risks associated with long-term VKA anticoagulation with a mechanical valve replacement. Despite the significantly higher rate of bioprosthetic structural valve deterioration observed in younger versus older patients,^{7–11,14,15} many patients choose to avoid a mechanical prosthesis because they are unwilling to consider long-term VKA therapy because of the inconvenience of monitoring, dietary restrictions, medication interactions, and the need to restrict participation in some types of athletic activity. A mechanical valve might be a prudent choice for patients for whom a second surgical procedure would involve very high risk (eg, those with prior radiation exposure). The availability of TAVI has changed the dynamics of the discussion of the trade-offs between mechanical and bioprosthetic valves in younger patients^{16–19} (Table 22).

Recommendation-Specific Supportive Text

1. The choice of valve prosthesis in each patient is based on consideration of several factors, including valve durability, expected hemodynamics for valve type and size, surgical or interventional risk, the potential need for long-term anticoagulation, and patient values and preferences. The trade-off between the risk of reintervention for bioprosthetic valve deterioration and the risk of long-term anticoagulation should be discussed. Some patients prefer to avoid repeat surgery and are willing to accept the risks and inconvenience of lifelong anticoagulant therapy. Other patients are unwilling to consider long-term anticoagulation because of the inconvenience of monitoring, the attendant dietary and medication interactions, and the need to restrict participation in some types of physical activity. The incidence of structural deterioration of a bioprosthesis is greater in younger patients, but the risk of bleeding from anticoagulation is higher in older patients. In patients with shortened longevity and/or multiple comorbidities, a bioprosthesis might be more appropriate. In women who desire subsequent pregnancy, the issue of anticoagulation during pregnancy is an additional consideration (see pregnancy-related issues in Section 13.5).^{20,21}
2. Anticoagulant therapy with VKA is necessary in all patients with a mechanical valve to prevent valve thrombosis and thromboembolic events. If anticoagulation is contraindicated or if the patient refuses VKA therapy, an alternative valve choice is appropriate. Newer anticoagulant agents have not been shown to be safe or effective in patients with mechanical heart valves.
3. Patients <50 years of age at the time of AVR incur a higher and earlier risk of bioprosthetic valve deterioration.^{4,10,14,22–24} Overall, the predicted 15-year risk of needing reoperation because of structural deterioration is 22% for patients 50 years of age, 30% for patients 40 years of age, and 50% for patients 20 years of age, although it is recognized that all bioprostheses are not alike in terms of durability.¹⁴ Anticoagulation with a VKA can be accomplished with acceptable risk in most patients <50 years of age, particularly in compliant patients with appropriate monitoring of INR levels. Thus, the balance between valve durability and risk of bleeding and thromboembolic events favors the choice of a mechanical valve in patients <50 years of age, unless anticoagulation is not desired, cannot be monitored, or is contraindicated.
4. Uncertainty and debate continue about which type of AVR is appropriate for patients 50 to 65 years of age. Newer surgical bioprosthetic valves may show greater freedom from structural deterioration, specifically in the older individual, although a high late mortality rate in these studies may preclude recognition of valve dysfunction.^{14–19} The risks of bleeding and thromboembolism with mechanical prostheses are low, especially in compliant patients with appropriate INR monitoring. Several studies have shown a survival advantage with a mechanical prosthesis in this age group. Alternatively, large retrospective observational studies have shown similar long-term survival rates in patients 50 to 69 years of age undergoing mechanical versus bioprosthetic valve replacement.^{22–24} In general, patients with mechanical valves experience a higher risk of bleeding caused by anticoagulation, whereas individuals who receive bioprosthetic valves experience a higher rate of reoperation because of structural deterioration of the prosthesis, as well as perhaps a decrease in survival rate.^{6,25–27} There are several other factors to consider in the choice of type of valve prosthesis (see Section 11.1). Ultimately, the choice of mechanical versus bioprosthetic valve replacement for all patients, but especially for those between 50 and 65 years of age, is a shared decision-making process that must account for the trade-offs between durability (and the need for reintervention), bleeding, and thromboembolism.¹
5. In patients >65 years of age at the time of bioprosthetic AVR, the likelihood of primary structural deterioration at 15 to 20 years is only about 10%.^{28–31} In addition, older patients are at higher

risk of bleeding complications related to VKA therapy and more often require interruption of VKA therapy for noncardiac surgical and interventional procedures. It is reasonable to use a bioprosthetic valve in patients >65 years of age to avoid the risks of anticoagulation because the durability of the valve exceeds the expected years of life.

6. Replacement of the aortic valve with a pulmonary autograft (the Ross procedure) is a complex operation involving replacement of the aortic valve by the patient's own pulmonic valve, along with placement of a pulmonic valve homograft. The Ross procedure allows the patient to avoid a prosthetic heart valve and the risks of anticoagulation and it provides excellent valve hemodynamics. However, both the pulmonic homograft in the pulmonic position and the pulmonary autograft (the neo-aortic valve) are at risk of valve degeneration. The failure of the Ross procedure is most often attributable to regurgitation of the neo-aortic valve in the second decade after the operation. In addition, at least half of pulmonic homograft valves require reintervention within 10 to 20 years. Calcification of the homograft and adhesions between the homograft and neo-aorta may increase the difficulty of reoperation. The Ross procedure typically is reserved for younger patients with appropriate anatomy and tissue characteristics for whom anticoagulation is either contraindicated or undesirable, and it is performed only at Comprehensive Valve Centers by surgeons experienced in this procedure.^{11–13,32}

3.2.4.2. Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate

Recommendations for Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate		
Referenced studies that support the recommendations are summarized in Online Data Supplement 11 to 13.		
COR	LOE	Recommendations
1	A	1. For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended. ^{1–3}
1	A	2. For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability. ^{1,4–8}
1	A	3. For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR. ^{1,4–10}

Recommendations for Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate (Continued)		
COR	LOE	Recommendations
1	B-NR	4. In asymptomatic patients with severe AS and an LVEF <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in Recommendations 1, 2, and 3 above. ^{1,2,4–10}
1	B-NR	5. For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated BNP (COR 2a indications for AVR), SAVR is recommended in preference to TAVI. ^{1–3,11}
1	A	6. For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve or vascular anatomy or other factors are not suitable for transfemoral TAVI, SAVR is recommended. ^{1–3,11}
1	A	7. For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life. ^{12,13,14,15}
1	C-EO	8. For symptomatic patients with severe AS for whom predicted post-TAVI or post-SAVR survival is <12 months or for whom minimal improvement in quality of life is expected, palliative care is recommended after shared decision-making, including discussion of patient preferences and values.
2b	C-EO	9. In critically ill patients with severe AS, percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVI.

Synopsis

In patients considering a bioprosthetic AVR, the next step is the choice between SAVR and TAVI. In patients with a high or prohibitive risk for SAVR (see Section 2.5), decision-making focuses on TAVI versus palliative care. When surgical risk is not high or prohibitive, procedure-specific impediments are assessed (Figure 3). When both SAVR and TAVI are options, a prime consideration is the limited data about TAVI durability. SAVR has been used for more than 50 years, with ample durability data available for specific valve types across different age groups. Currently, robust durability data for TAVI extend to only about 5 years. SAVR valve deterioration typically occurs after >10 years, so longer-term TAVI durability data are needed. A key factor in decision-making is the ratio of patient life expectancy to known valve durability, with patient age often used as a surrogate for life expectancy. For a woman in the United States, the average additional expected years of life are 25 at age 60 years, 17 at age 70 years, and 10 at age 80 years. For a man, expected additional years of life are 22 at age 60 years, 14 at age 70 years, and 8 at age 80 years. The age break-points shown in these recommendations reflect these

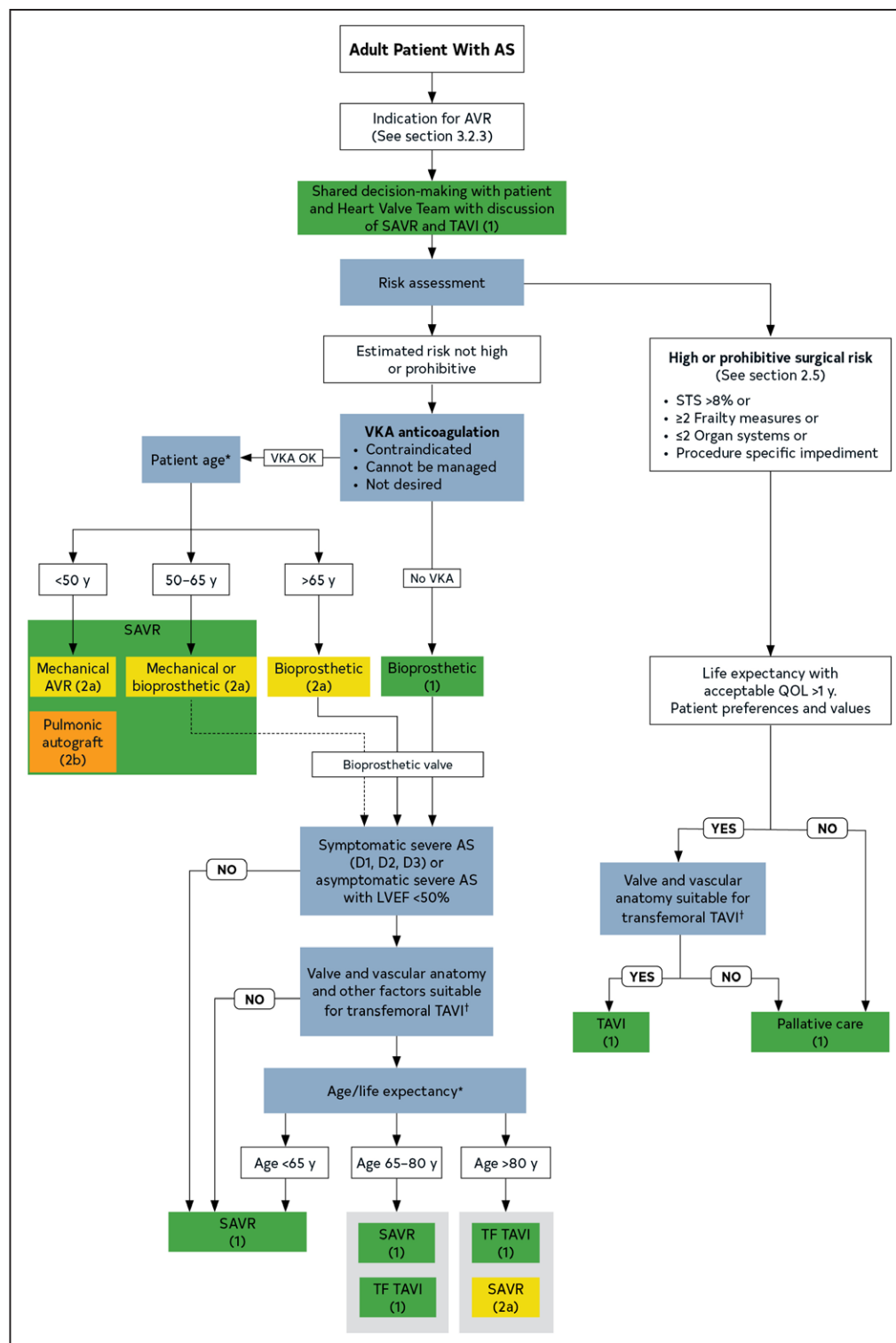


Figure 3. Choice of SAVR versus TAVI when AVR is indicated for valvular AS.

Colors correspond to Table 2. *Approximate ages, based on US Actuarial Life Expectancy tables, are provided for guidance. The balance between expected patient longevity and valve durability varies continuously across the age range, with more durable valves preferred for patients with a longer life expectancy. Bioprosthetic valve durability is finite (with shorter durability for younger patients), whereas mechanical valves are very durable but require lifelong anticoagulation. Long-term (20-y) data on outcomes with surgical bioprosthetic valves are available; robust data on transcatheter bioprosthetic valves extend to only 5 years, leading to uncertainty about longer-term outcomes. The decision about valve type should be individualized on the basis of patient-specific factors that might affect expected longevity. †Placement of a transcatheter valve requires vascular anatomy that allows transfemoral delivery and the absence of aortic root dilation that would require surgical replacement. Valvular anatomy must be suitable for placement of the specific prosthetic valve, including annulus size and shape, leaflet number and calcification, and coronary ostial height. See ACC Expert Consensus Statement.²⁰ AS indicates aortic stenosis; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; QOL, quality of life; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TF, transfemoral; and VKA, vitamin K antagonist.

statistical averages and serve as the starting point for shared decision-making, not as absolute values for chronological age. Some younger patients with comorbid conditions have a limited life expectancy, whereas some older patients have a longer-than-average life expectancy. Decision-making should be individualized on the basis of patient-specific factors that affect longevity or quality of life, such as comorbid cardiac and noncardiac conditions, frailty, dementia, and other factors. In addition, the choice of implantation approach is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and against each approach and the potential need for and risks associated with valve reintervention.^{16–19}

Recommendation-Specific Supportive Text

1. SAVR has demonstrated excellent durability and outcomes for both mechanical and bioprosthetic valves. Earlier RCTs comparing SAVR and TAVI in patients with a higher surgical risk included only older patients, with a mean age in the mid-80s. More recent RCTs that included patients at low to intermediate surgical risk had a mean age in the mid-70s, but there were very few patients <65 years of age, so the evidence base cannot be extrapolated to these patients. In addition, valve durability is of higher priority in younger patients, who typically have a longer life expectancy and lower surgical risk. As longer-term data on TAVI valve durability become available, the age range for recommending TAVI may shift, but at this time the most prudent course, based on the published evidence, is to recommend SAVR for adults <65 years of age unless life expectancy is limited by comorbid cardiac or noncardiac conditions. The final choice of implantation approach is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and against each approach and the potential need for and risks associated with valve reintervention. There are no data for the use of TAVI in patients <65 years of age.²¹
2. Both SAVR and TAVI are effective approaches to AVR in adults 65 to 80 years of age. Patients enrolled in RCTs of TAVI versus SAVR had high-velocity severe AS (Stage D1). However, less robust data from observational studies and registry data are encouraging with regard to TAVI for symptomatic patients with low-flow, low-gradient severe AS (Stages D2 and D3). Thus, these guidelines make the same recommendations for symptomatic patients with confirmed severe AS

regardless of flow rate. TAVI has a slightly lower mortality risk and is associated with a shorter hospital length of stay, more rapid return to normal activities, lower risk of transient or permanent AF, less bleeding, and less pain than SAVR. On the other hand, SAVR is associated with a lower risk of paravalvular leak, less need for valve reintervention, and less need for a permanent pacemaker. When the choice of SAVR or TAVI is being made in an individual patient between 65 and 80 years of age, other factors, such as vascular access, comorbid cardiac and noncardiac conditions that affect risk of either approach, expected functional status and survival after AVR, and patient values and preferences, must be considered. The choice of mechanical or bioprosthetic SAVR (Section 11) versus a TAVI is an important consideration and is influenced by durability considerations, because durability of transcatheter valves beyond 5 to 6 years is not yet known.²

3. TAVI is a safe and effective procedure for treatment of severe symptomatic AS in all adults regardless of estimated surgical risk. The mortality rate for transfemoral TAVI is lower than that for SAVR, with a HR of 0.88 and a 95% CI of 0.78 to 0.99 in a meta-analysis of RCTs. TAVI also is associated with a lower risk of stroke (HR: 0.81; 95% CI: 0.68–0.98; $P=0.028$), major bleeding, and AF, as well as a shorter hospital length of stay, less pain, and more rapid return to normal activities.³ Compared with SAVR, TAVI results in higher rates of vascular complications, paravalvular regurgitation, permanent pacemaker implantation, and valve intervention, but most patients will consider that the advantages of TAVI outweigh these disadvantages. TAVI valves are durable to at least 5 years, and the limited data on TAVI durability are of less concern to most patients >80 years of age because the valve durability is likely to be longer than the patient's life expectancy.²² If significant valve deterioration does occur, a second TAVI within the first prosthesis, (called a valve-in-valve TAVI), is likely to be possible. When a transfemoral approach is not possible, other factors, such as alternative vascular access, comorbid cardiac and noncardiac conditions, expected functional status and survival after AVR, and patient values and preferences, must be considered. The specific choice of a balloon-expandable valve or self-expanding valve depends on patient anatomy and other considerations.^{23–28}
4. An LVEF <50% in a patient with severe AS is a COR 1 indication for AVR, so the choice of TAVI versus SAVR in these patients is based on the same considerations as in patients with symptoms

attributable to severe AS. From a pathophysiologic point of view, the reasons for thinking that TAVI might be especially beneficial with severe AS and a low LVEF are the avoidance of myocardial ischemia with an open surgical procedure and the greater reduction in afterload with a larger effective valve area. However, outcome data from RCTs show that a low LVEF also is a risk factor for adverse outcomes even with TAVI.²⁹ The final choice of implantation approach is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and against each approach and the potential need for and risks associated with valve reintervention. Studies on the potential benefit of TAVI in patients with moderate AS and LV systolic dysfunction are in progress.

5. Published RCTs comparing TAVI and SAVR included only patients with symptoms attributable to severe AS. Asymptomatic patients with COR 2a indications for AVR should either undergo SAVR or wait until a COR 1 indication is present before intervention. The recommendation for SAVR in preference to TAVI includes asymptomatic patients for whom AVR is being considered because of an abnormal exercise blood pressure response, an elevated serum BNP level, rapid hemodynamic progression, or very severe AS with a velocity of ≥ 5 m/s. The final choice of implantation approach is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and against each approach and the potential need for and risks associated with valve reintervention.^{30–32}
6. Published RCTs have focused primarily on TAVI via the transfemoral vascular access route. The mortality rate has been higher with TAVI by nonfemoral access routes than with SAVR, possibly because of the access approach itself, but more likely because of the higher comorbidity burden and risk in patients with vascular disease severe enough to preclude transfemoral access. When transfemoral TAVI is not feasible, SAVR or palliative care options should be included in the shared decision-making discussion. The final choice of implantation approach is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and against each approach and the potential need for and risks associated with valve reintervention.^{1,33}

7. TAVI was compared with standard medical therapy in a prospective RCT of patients with severe symptomatic AS who were deemed inoperable.^{12,14,34} The rate of all-cause death at 2 years was lower with TAVI (43.3%) (HR: 0.58; 95% CI: 0.36–0.92; $P=0.02$) than with standard medical therapy (68%).^{12,14,34} Standard therapy included percutaneous aortic balloon dilation in 84%. There was a reduction in repeat hospitalization with TAVI (55% versus 72.5%; $P<0.001$). In addition, only 25.2% of survivors were in New York Heart Association (NYHA) class III or IV 1 year after TAVI, compared with 58% of patients receiving standard therapy ($P<0.001$). However, the rate of major stroke was higher with TAVI than with standard therapy at 30 days (5.05% versus 1.0%; $P=0.06$) and remained higher at 2 years (13.8% versus 5.5%; $P=0.01$). Major vascular complications occurred in 16.2% with TAVI versus 1.1% with standard therapy ($P<0.001$).^{12,14,34} Similarly, in a nonrandomized study of 489 patients with severe symptomatic AS and extreme surgical risk treated with a self-expanding TAVI valve, the rate of all-cause death at 12 months was 26% with TAVI, compared with an expected mortality rate of 43% if patients had been treated medically.¹³ The final choice of TAVI versus palliative care is based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indication, risks, and benefits for and against each approach.
8. The survival and symptom reduction benefit of TAVI is seen only in appropriately selected patients. Baseline clinical factors associated with a poor outcome after TAVI include advanced age, frailty, smoking or chronic obstructive pulmonary disease, pulmonary hypertension, liver disease, prior stroke, anemia, and other systemic conditions. The STS estimated surgical risk score provides a useful measure of the extent of patient comorbidities and may help identify which patients will benefit from TAVI. Patients with a mechanical impediment to SAVR, such as a porcelain aorta or prior chest radiation damage, may have better outcomes after TAVI than do frail patients or those with moderate to severe disease in more than one other organ system.^{12,14,34} The likely benefits and risks of TAVI are considered in weighing the risk–benefit ratio of intervention in an individual patient. TAVI is not recommended in patients with 1) a life expectancy of <1 year even with a successful procedure or 2) those with a chance of “survival with benefit” of $<25\%$ at 2 years.

Table 14. A Simplified Framework With Examples of Factors Favoring SAVR, TAVI, or Palliation Instead of Aortic Valve Intervention

	Favors SAVR	Favors TAVI	Favors Palliation
Age/life expectancy*	Younger age/longer life expectancy	Older age/fewer expected remaining years of life	Limited life expectancy
Valve anatomy	BAV Subaortic (LV outflow tract) calcification Rheumatic valve disease Small or large aortic annulus†	Calcific AS of a trileaflet valve	
Prosthetic valve preference	Mechanical or surgical bioprosthetic valve preferred Concern for patient–prosthesis mismatch (annular enlargement might be considered)	Bioprosthetic valve preferred Favorable ratio of life expectancy to valve durability TAVI provides larger valve area than same size SAVR	
Concurrent cardiac conditions	Aortic dilation‡ Severe primary MR Severe CAD requiring bypass grafting Septal hypertrophy requiring myectomy AF	Severe calcification of the ascending aorta (“porcelain” aorta)	Irreversible severe LV systolic dysfunction Severe MR attributable to annular calcification
Noncardiac conditions		Severe lung, liver, or renal disease Mobility issues (high procedural risk with sternotomy)	Symptoms likely attributable to noncardiac conditions Severe dementia Moderate to severe involvement of ≥2 other organ systems
Frailty	Not frail or few frailty measures	Frailty likely to improve after TAVI	Severe frailty unlikely to improve after TAVI
Estimated procedural or surgical risk of SAVR or TAVI	SAVR risk low TAVI risk high	TAVI risk low to medium SAVR risk high to prohibitive	Prohibitive SAVR risk (>15%) or post-TAVI life expectancy <1 y
Procedure-specific impediments	Valve anatomy, annular size, or low coronary ostial height precludes TAVI Vascular access does not allow transfemoral TAVI	Previous cardiac surgery with at-risk coronary grafts Previous chest irradiation	Valve anatomy, annular size, or coronary ostial height precludes TAVI Vascular access does not allow transfemoral TAVI
Goals of Care and patient preferences and values	Less uncertainty about valve durability Avoid repeat intervention Lower risk of permanent pacer Life prolongation Symptom relief Improved long-term exercise capacity and QOL Avoid vascular complications Accepts longer hospital stay, pain in recovery period	Accepts uncertainty about valve durability and possible repeat intervention Higher risk of permanent pacer Life prolongation Symptom relief Improved exercise capacity and QOL Prefers shorter hospital stay, less postprocedural pain	Life prolongation not an important goal Avoid futile or unnecessary diagnostic or therapeutic procedures Avoid procedural stroke risk Avoid possibility of cardiac pacer

*Expected remaining years of life can be estimated from US Actuarial Life Expectancy tables. The balance between expected patient longevity and valve durability varies continuously across the age range, with more durable valves preferred for patients with a longer life expectancy. Bioprosthetic valve durability is finite (with shorter durability for younger patients), whereas mechanical valves are very durable but require lifelong anticoagulation. Long-term (20-y) data on outcomes with surgical bioprosthetic valves are available; robust data on transcatheter bioprosthetic valves extend only to 5 y, leading to uncertainty about longer-term outcomes. The decision about valve type should be individualized on the basis of patient-specific factors that might affect expected longevity.

†A large aortic annulus may not be suitable for currently available transcatheter valve sizes. With a small aortic annulus or aorta, a surgical annulus-enlarging procedure may be needed to allow placement of a larger prosthesis and avoid patient–prosthesis mismatch.

‡Dilation of the aortic sinuses or ascending aorta may require concurrent surgical replacement, particularly in younger patients with a BAV.

AF indicates atrial fibrillation; AS, aortic stenosis; BAV, bicuspid aortic valve; CAD, coronary artery disease; LV, left ventricular; MR, mitral regurgitation; QOL, quality of life; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

Modified from Burke et al.¹⁶

9. Percutaneous aortic balloon dilation has a role in treating children, adolescents, and young adults with AS, but its role in treating older patients is very limited. The mechanism by which balloon dilation modestly reduces the severity of

stenosis in older patients is fracture of calcific deposits within the valve leaflets and, to a minor degree, stretching of the annulus and separation of the calcified or fused commissures. Immediate hemodynamic results include a

moderate reduction in the transvalvular pressure gradient, but the postdilation valve area rarely exceeds 1.0 cm². Despite the modest change in valve area, an early symptomatic improvement usually occurs. However, serious acute complications, including acute severe AR, restenosis, and clinical deterioration, occur within 6 to 12 months in most patients. Therefore, in patients with AS, percutaneous aortic balloon dilation is not a substitute for AVR. Some clinicians contend that, despite the procedural morbidity and mortality rates and limited long-term results, percutaneous aortic balloon dilation can have a temporary role in the management of some symptomatic patients, such as those patients with severe AS and refractory pulmonary edema or cardiogenic shock, who might benefit from percutaneous aortic balloon dilation as a “bridge” to TAVI or SAVR. However, this approach is used less frequently given the availability and success of immediate TAVI even in very high-risk patients (Table 14).^{35–38}

4. AORTIC REGURGITATION

4.1. Acute Aortic Regurgitation

Acute aortic regurgitation (AR) may result from abnormalities of the valve, most often endocarditis, or abnormalities of the aorta, primarily aortic dissection. Acute AR may also occur as an iatrogenic complication of a transcatheter procedure or after blunt chest trauma. The acute volume overload on the LV usually results in severe pulmonary congestion, as well as a low forward cardiac output. Urgent diagnosis and rapid intervention are lifesaving.

4.1.1. Diagnosis of Acute AR

TTE or TEE is indispensable in confirming the presence, severity, and etiology of acute AR; determining whether there is rapid equilibration of the aortic and LV diastolic pressures; visualizing the aortic root; and evaluating LV size and systolic function.^{1,2} A short deceleration time on the aortic flow velocity curve and early closure of the mitral valve are indicators of markedly elevated LV end-diastolic pressure. A pressure half-time of <300 ms on the AR velocity curve indicates rapid equilibration of the aortic and LV diastolic pressures. The degree of holodiastolic flow reversal in the aortic arch, in comparison with the forward systolic flow, provides a quick semiquantitative estimate of regurgitant fraction. Acute severe AR caused by aortic dissection is a surgical emergency. CT imaging is the primary approach for diagnosis of

acute aortic dissection because it is highly accurate and continuously available at most medical centers. MRI is rarely used in the acute setting because of patient instability. TEE may be used when CT imaging is unavailable and is helpful in intraoperative assessment of aortic valve function before and after the surgical intervention. The sensitivity and specificity of TTE for diagnosis of Type A³ aortic dissection are only 60% to 80%, whereas TEE has a sensitivity of 98% to 100% and a specificity of 95% to 100%. Angiography should be considered only when the diagnosis cannot be determined by noninvasive imaging or when the differential diagnosis is an acute coronary syndrome.

4.1.2. Intervention for Acute AR

In patients with acute severe AR resulting from IE or aortic dissection, medical therapy to reduce LV afterload may allow temporary stabilization, but surgery should not be delayed, especially if there is hypotension, pulmonary edema, or evidence of low flow.^{1–4} Intra-aortic balloon counterpulsation is contraindicated in patients with acute severe AR.⁵ Beta blockers are often used in treating aortic dissection. However, these agents should be used very cautiously, if at all, for other causes of acute AR because they will block the compensatory tachycardia and could precipitate a marked reduction in blood pressure.

4.2. Stages of Chronic AR

The most common causes of chronic severe AR in the United States and other high-income countries are BAV disease and primary diseases of the ascending aorta or the sinuses of Valsalva. Rheumatic heart disease is the leading cause of AR in many low- to middle-income countries. With calcific valve disease, regurgitation often accompanies AS, but the degree of regurgitation usually is mild to moderate, not severe. In most 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 an accurate diagnosis of the cause and stage of the disease process. Table 15 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 (Stage D) AR. 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.

Table 15. Stages of Chronic AR

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AR	BAV (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 BAV (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 Regurgitant volume <30 mL/beat Regurgitant fraction <30% ERO <0.10 cm ² Angiography grade 1 Moderate AR: Jet width 25%–64% of LVOT Vena contracta 0.3–0.6 cm Regurgitant volume 30–59 mL/beat Regurgitant fraction 30% to 49% ERO 0.10–0.29 cm ² 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 Regurgitant volume ≥60 mL/beat Regurgitant fraction ≥50% ERO ≥0.3 cm ² Angiography grade 3 to 4 In addition, diagnosis of chronic severe AR requires evidence of LV dilation	C1: Normal LVEF (>55%) and mild to moderate LV dilation (LVESD <50 mm) C2: Abnormal LV systolic function with depressed LVEF (≤55%) or severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m ²)	None; exercise testing is reasonable to confirm symptom status
D	Symptomatic severe AR	Calcific valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes Previous IE with abnormal leaflet closure or perforation	Severe AR: Doppler jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta Regurgitant volume ≥60 mL/beat Regurgitant fraction ≥50% ERO ≥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 >55%), mild to moderate LV dysfunction (LVEF 40% to 55%), 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; BAV, bicuspid aortic valve; ERO, effective regurgitant orifice; HF, heart failure; IE, infective endocarditis; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; and LVOT, left ventricular outflow tract.

4.3. Chronic AR

4.3.1. Diagnosis of Chronic AR

Recommendations for Diagnostic Testing of Chronic AR Referenced studies that support the recommendations are summarized in Online Data Supplement 14.		
COR	LOE	Recommendations
1	B-NR	1. In patients with signs or symptoms of AR, TTE is indicated for assessment of the cause and severity of regurgitation, LV size and systolic function, prognosis, and timing of valve intervention. ^{1–19}
1	B-NR	2. In patients with a BAV or with known dilation of the aortic sinuses or ascending aorta, TTE is indicated to evaluate the presence and severity of AR. ¹
1	B-NR	3. In patients with moderate or severe AR and suboptimal TTE images or a discrepancy between clinical and TTE findings, TEE, CMR, or cardiac catheterization is indicated for the assessment of LV systolic function, systolic and diastolic volumes, aortic size, and AR severity. ^{20–25}

Synopsis

TTE provides diagnostic information about the etiology and mechanism of AR (including valve reparability), severity of regurgitation, morphology of the ascending aorta, and LV response to the increases in preload and afterload. Imaging with TEE, CMR, or aortic angiography provides additional information when needed.

Recommendation-Specific Supportive Text

- Although qualitative measures of AR severity are adequate in many situations, when AR is significant (Stages B and C), quantitative measures of regurgitant volume and effective regurgitant orifice (ERO) area¹ are better predictors of clinical outcome.^{2,3} Measures of LV systolic function (LVEF or fractional shortening) and LV end-systolic dimension (LVESD) or LV end-systolic volume are predictive of the development of HF symptoms or death in initially asymptomatic patients (Stages B and C1) and are significant determinants of survival and functional results after surgery in asymptomatic and symptomatic patients (Stages C2 and D).^{2–18,26} Symptomatic patients (Stage D) with normal LVEF have a significantly better long-term postoperative survival rate than those with depressed systolic function.
- Auscultation has high specificity for detecting AR but low sensitivity and diagnostic accuracy.²⁷ TTE can identify AR in patients who have been deemed to be at risk on the basis of the presence of known aortic dilation or a condition associated with abnormal aortic valve function, such as a BAV.

- TTE and CMR are useful for evaluating patients in whom there is discordance between clinical assessment and severity of AR by TTE or when TTE images are suboptimal. CMR imaging provides accurate and reproducible measures of regurgitant volume and regurgitant fraction in patients with AR, as well as assessment of aortic morphology, LV volume, and LV systolic function. Cardiac catheterization with LV and aortic angiography, as well as quantitation of regurgitation severity, is another option.^{20–25,28–30}

4.3.2. Medical Therapy

Recommendations for Medical Therapy of Chronic AR Referenced studies that support the recommendations are summarized in Online Data Supplement 14.		
COR	LOE	Recommendations
1	B-NR	1. In asymptomatic patients with chronic AR (Stages B and C), treatment of hypertension (systolic blood pressure >140 mmHg) is recommended. ^{1–3}
1	B-NR	2. In patients with severe AR who have symptoms and/or LV systolic dysfunction (Stages C2 and D) but a prohibitive surgical risk, GDMT for reduced LVEF with ACE inhibitors, ARBs, and/or sacubitril/valsartan is recommended. ⁴

Synopsis

There is no evidence that vasodilating drugs reduce severity of AR or alter the disease course in patients with significant AR in the absence of systemic hypertension. Recommendations for GDMT for hypertension and HF apply to patients with chronic asymptomatic AR, as for the general population.

Recommendation-Specific Supportive Text

- Severe AR is associated with a wide pulse pressure, such that systolic blood pressure is higher than in patients without AR even when systemic vascular resistance is normal. Transaortic stroke volume increases further with medications that lower heart rate, such as beta blockers, which may result in a paradoxical apparent increase in blood pressure. Vasodilating drugs, such as ACE inhibitors or ARBs, do not affect heart rate and thus may reduce systolic blood pressure without a substantial reduction in diastolic blood pressure in patients with chronic AR.^{1,2,5–8}
- In symptomatic patients who are candidates for surgery, medical therapy is not a substitute for AVR. However, medical therapy is helpful for alleviating symptoms in patients who are considered to be at very high surgical risk because of concomitant comorbid medical conditions.^{5,9}

4.3.3. Timing of Intervention

Recommendations for Timing of Intervention for Chronic AR Referenced studies that support the recommendations are summarized in Online Data Supplement 15 to 17.		
COR	LOE	Recommendations
1	B-NR	1. In symptomatic patients with severe AR (Stage D), aortic valve surgery is indicated regardless of LV systolic function. ¹⁻⁷
1	B-NR	2. In asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF ≤55%) (Stage C2), aortic valve surgery is indicated if no other cause for systolic dysfunction is identified. ^{3,5,8-12}
1	C-EO	3. In patients with severe AR (Stage C or D) who are undergoing cardiac surgery for other indications, aortic valve surgery is indicated.
2a	B-NR	4. In asymptomatic patients with severe AR and normal LV systolic function (LVEF >55%), aortic valve surgery is reasonable when the LV is severely enlarged (LVESD >50 mm or indexed LVESD >25 mm/m ²) (Stage C2). ^{10,11,13-24}
2a	C-EO	5. In patients with moderate AR (Stage B) who are undergoing cardiac or aortic surgery for other indications, aortic valve surgery is reasonable.
2b	B-NR	6. In asymptomatic patients with severe AR and normal LV systolic function at rest (LVEF >55%; Stage C1) and low surgical risk, aortic valve surgery may be considered when there is a progressive decline in LVEF on at least 3 serial studies to the low-normal range (LVEF 55% to 60%) or a progressive increase in LV dilation into the severe range (LV end-diastolic dimension [LVEDD] >65 mm). ^{12,16,17,20,25-28}
3: Harm	B-NR	7. In patients with isolated severe AR who have indications for SAVR and are candidates for surgery, TAVI should not be performed. ²⁹⁻³²

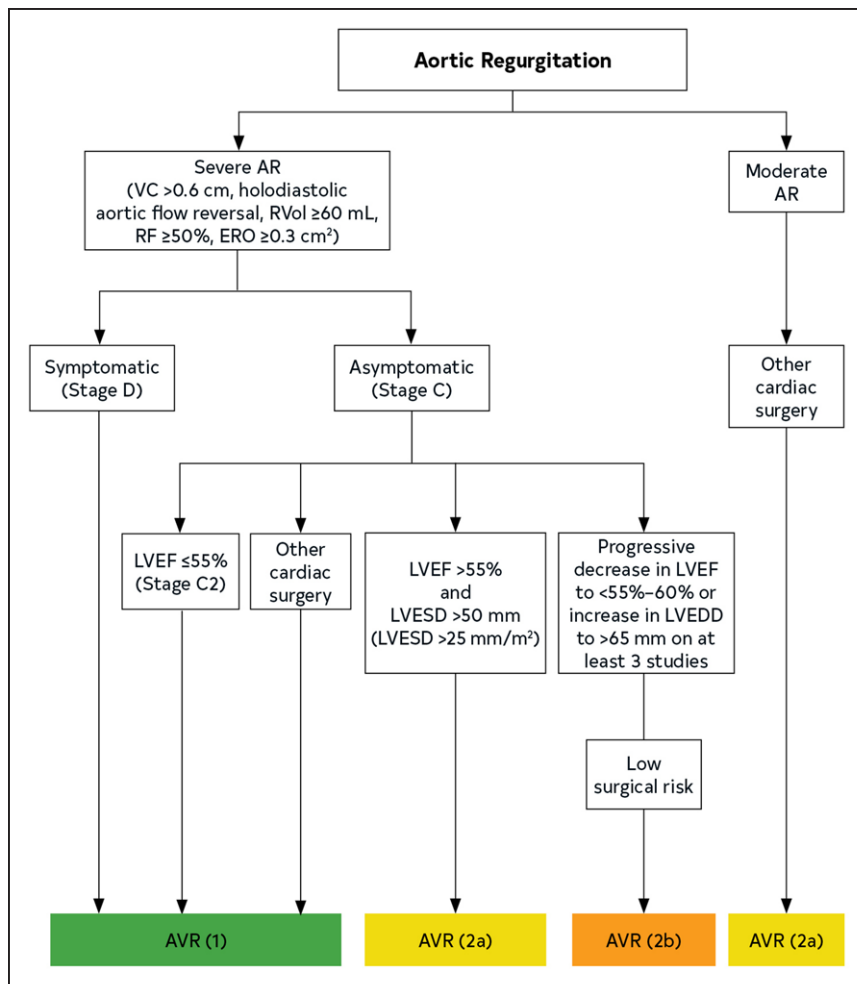
Synopsis

Most patients with indications for surgery for chronic severe AR require valve replacement with a mechanical or bioprosthetic valve (Figure 4). Preservation of the native aortic valve ("valve sparing") may be possible in selected patients with favorable valve anatomy who are undergoing surgical replacement of the aortic sinuses and/or ascending aorta.³³⁻³⁹ Although advances are occurring in primary aortic valve repair,^{37,40-42} this approach is not yet generalizable, and durability is not known. Current recommendations for AVR related to severity of LV dilation are based on measurement of LV short-axis diameters. There are limited data demonstrating prognostic value of LV volume measurements in chronic AR using left ventriculography,⁴³ 2D echocardiography,^{18,44} and CMR.^{45,46} Normal limits for LV volumes have been determined, as have criteria for severe LV dilation, but these values differ between 2D echocardiography, 3D echocardiography, and CMR,^{47,48} and there are insufficient data on the relationship between LV volumes and outcomes of

patients with AR. This is an area in need of further investigation. Other markers of LV dysfunction and remodeling, such as global longitudinal strain and circulation biomarkers,^{44,46,49-51} likewise require additional clinical outcome studies.

Recommendation-Specific Supportive Text

1. Symptoms are an important indication for AVR in patients with chronic severe AR, and the most important aspect of the clinical evaluation is taking a careful, detailed history to elicit symptoms or diminution of exercise capacity. Patients with chronic severe AR who develop symptoms have a high risk of death if AVR is not performed,⁵² and survival and functional status after AVR are related to the severity of preoperative symptoms, assessed either subjectively or objectively with exercise testing.¹⁻⁴ Even among symptomatic patients with a severe reduction in LVEF (<35%), AVR results in improved survival rate.⁵⁻⁷
2. LV systolic function is an important determinant of survival and functional status after AVR.^{3-5,8,9,12,53-61} Outcomes are optimal when surgery is performed before LVEF decreases below 55%.^{16,25,26} In asymptomatic patients with LV systolic dysfunction, postoperative outcomes are better if AVR is performed before onset of symptoms.⁵³
3. Patients with chronic severe AR may be referred for other types of cardiac surgery, such as CABG, mitral valve surgery, or surgery for correction of dilation of the aortic root or ascending aorta. In these patients, AVR will prevent both the hemodynamic consequences of persistent AR during the perioperative period and the possible need for a second cardiac operation in the near future. Patients undergoing surgical repair or replacement of the aortic root or ascending aorta may be candidates for aortic valve-sparing procedures.³³⁻³⁹
4. LVESD in patients with chronic AR reflects both the severity of the LV volume overload and the degree of LV systolic shortening.^{54,62} An elevated LVESD often reflects LV systolic dysfunction with a depressed LVEF. If LVEF is normal, an increased LVESD indicates a significant degree of LV remodeling and is associated with subsequent development of symptoms and/or LV systolic dysfunction and an increased mortality rate after AVR.^{17,20,21} Most studies have used unadjusted LVESD, but indexing for body size is important, particularly in women or small patients.^{13,19,52} Recent data indicate that the LVESD index threshold for optimal postoperative survival may be even smaller than 25 mm/m²,¹⁴⁻¹⁶ but more outcome data, and ideally an RCT, of earlier intervention are needed.

**Figure 4. Timing of intervention for AR.**

Colors correspond to Table 2. AR indicates aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic dimension; ERO, effective regurgitant orifice; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; and VC, vena contracta

LV volumes may be a more sensitive predictor of cardiac events than LVESD index in asymptomatic patients,¹⁸ but more data are needed to determine the threshold values of LV systolic volume that best predict postoperative outcomes.

5. In patients with moderate AR who are undergoing other forms of cardiac surgery, such as CABG, mitral valve surgery, or replacement of the ascending aorta, the decision to intervene on the aortic valve concurrently includes consideration of several factors, including aortic valve anatomy, aortic root size and shape, regurgitant severity, other comorbidities, and patients' preferences and values. Patients undergoing surgical repair or replacement of the aortic root or ascending aorta may be candidates for a valve-sparing procedure.^{33–39}
6. LVESD, a marker of the severity of LV volume overload in patients with chronic AR, is significantly associated with clinical outcomes in asymptomatic patients, and progressive increases in LVESD are associated with subsequent need for surgery.^{16,17,20,25–28} In asymptomatic patients, it is

important to ensure that apparent changes in LV size or LVEF are not due simply to measurement or physiological variability. In addition, confirmation of severe regurgitation by quantitative measures of AR severity with TTE, TEE, or, when needed, CMR provides confidence that AR is the cause of LV dilation or decrease in LVEF. When there is an apparent significant fall in EF or increase in LV size, repeat imaging typically is performed at 3- to 6-month intervals unless there is clinical deterioration.

7. TAVI for isolated chronic AR is challenging because of dilation of the aortic annulus and aortic root and, in many patients, lack of sufficient leaflet calcification. Risks of TAVI for treatment of AR include transcatheter valve migration and significant paravalvular leak.^{29–32} TAVI is rarely feasible, and then only in carefully selected patients with severe AR and HF who have a prohibitive surgical risk and in whom valvular calcification and annular size are appropriate for a transcatheter approach.

5. BICUSPID AORTIC VALVE

5.1. BAV and Associated Aortopathy

5.1.1. Diagnosis and Follow-Up of BAV

5.1.1.1. Diagnostic Testing: Initial Diagnosis

Recommendations for Diagnostic Testing: Initial Diagnosis of BAV Referenced studies that support the recommendations are summarized in Online Data Supplement 18.		
COR	LOE	Recommendations
1	B-NR	1. In patients with a known BAV, TTE is indicated to evaluate valve morphology, measure severity of AS and AR, assess the shape and diameter of the aortic sinuses and ascending aorta, and evaluate for the presence of aortic coarctation for prediction of clinical outcome and to determine timing of intervention. ¹⁻⁴
1	C-LD	2. In patients with BAV, CMR angiography or CT angiography is indicated when morphology of the aortic sinuses, sinotubular junction, or ascending aorta cannot be assessed accurately or fully by echocardiography. ^{4,5}
2b	B-NR	3. In first-degree relatives of patients with a known BAV, a screening TTE might be considered to look for the presence of a BAV or asymptomatic dilation of the aortic sinuses and ascending aorta. ⁶

Synopsis

BAV is a common congenital anomaly that affects 0.5% to 2.0% of adults with a 3:1 male-to-female predominance.¹ Patients with BAV may develop isolated aortic valve disease, including isolated AR, AS, or a combination of the two. Aortic aneurysms have been reported in 20% to 40% of patients with BAV.¹ This aortopathy can occur independent of valve function and consists of dilation of the aortic sinuses, the ascending aorta, or the arch. Therefore, patients with BAV require careful evaluation of both the aortic valve and the aorta throughout their lifetimes (Figure 5).

Recommendation-Specific Supportive Text

- Many patients with BAV will develop AS or AR over their lifetimes. In a recent meta-analysis of natural history studies of patients with BAV, 13% to 30% of patients developed moderate or greater AR and 12% to 37% developed moderate or greater AS during follow-up.¹ TTE usually is adequate for evaluation of aortic valve anatomy and hemodynamics. TEE provides improved 2D and 3D images if needed. Aortic enlargement at the level of the sinuses or proximal ascending aorta has been reported in 20% to 40% of patients with BAV,¹ and some develop severe aneurysmal dilation and are at increased risk of aortic dissection.^{2,3,7-10} Aortic measurements are reported at the aortic annulus, sinuses of Valsalva, sinotubular junction, and mid-ascending aorta. Doppler interrogation

of the proximal descending aorta and abdominal aorta should also be performed to evaluate for the presence of aortic coarctation, which is associated with BAV in a subset of patients, although a coarctation also can be detected by comparing arm and leg blood pressures.

- CT angiography or CMR provides better images of the aortic sinuses, sinotubular junction, or ascending aorta when TTE does not adequately visualize the sinus and proximal 5 to 6 cm of the ascending aorta. The choice of CMR versus CT angiography depends on patient preference, insurance coverage, institutional expertise, and consideration of radiation exposure.
- In about 20% to 30% of patients with a BAV, other family members also have a BAV and/or an associated aortopathy. A specific genetic cause has not been identified, and the patterns of inheritance are variable. Imaging can identify the presence of a BAV and aortic dilation, but there is a paucity of data on the cost-effectiveness of this approach and whether earlier diagnosis would improve long-term clinical outcomes.^{6,11}

5.1.1.2. Diagnostic Testing: Routine Follow-Up

Recommendations for Diagnostic Testing: Routine Follow-Up of Patients With a BAV Referenced studies that support the recommendations are summarized in Online Data Supplement 18.		
COR	LOE	Recommendations
2a	C-LD	1. In patients with BAV and a diameter of the aortic sinuses or ascending aorta of ≥ 4.0 cm, lifelong serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or CT angiography is reasonable, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. ¹⁻⁵
2a	B-NR	2. In patients with a BAV who have undergone AVR, continued lifelong serial interval imaging of the aorta is reasonable if the diameter of the aortic sinuses or ascending aorta is ≥ 4.0 cm. ^{6,7}

Synopsis

Patients with BAV with and without associated aortic aortopathy require lifelong surveillance. Because progression of valve disease and growth of the aorta can occur in the absence of symptoms, diagnostic imaging plays an integral role in the surveillance process.

Recommendation-Specific Supportive Text

- Aortopathy is present in approximately 20% to 40% of patients with a BAV and is associated with dilation of the aortic sinuses, the ascending aorta, and/or the arch.¹ In a retrospective case series of 918 patients with BAV followed for 2 to 12 years

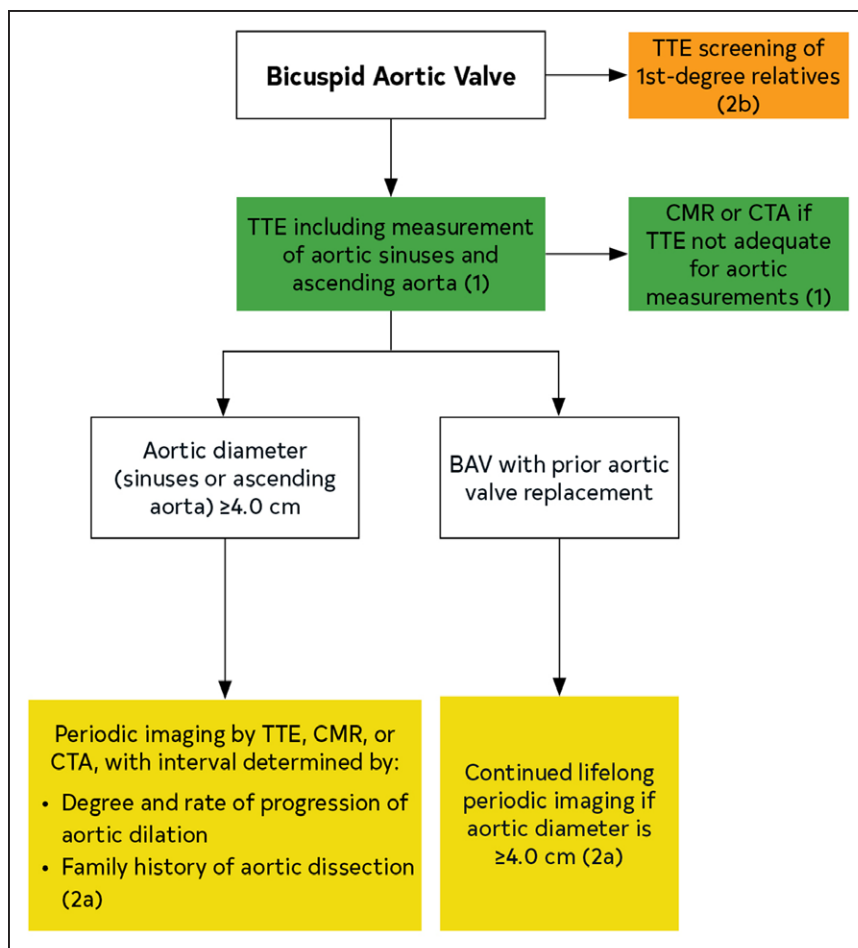


Figure 5. Intervals for imaging the aorta in patients with a BAV.

Colors correspond to Table 2. BAV indicates bicuspid aortic valve; CTA, computed tomographic angiography; CMR, cardiac magnetic resonance; TTE, transthoracic echocardiography.

with serial imaging, 47% required valve surgery but only 3.8% required aortic grafting without valve replacement, and <0.1% had aortic dissection.⁵ In a systematic review of 13 studies with >11 000 patients with a BAV, aortic dilation was present in 20% to 40%, but only 0.4% suffered aortic dissection.¹ Aortic imaging at least annually is prudent in patients with BAV and significant aortic dilation (>4.5 cm) to determine the appropriate timing of surgical intervention. Patients with risk factors that increase the risk of aortic dissection, such as a rapid rate of change in aortic diameter or a family history of aortic dissection, may also require more frequent monitoring. In patients with milder dilation that shows no change on sequential studies and with a negative family history, a longer interval between imaging studies is appropriate.^{1–4,8,9}

- In a retrospective review of 1286 patients with a BAV who underwent isolated AVR with a median of 12 years of follow-up, subsequent aortic dissection occurred in 1%, ascending aortic replacement surgery was needed in 0.9%, and progressive aortic enlargement was noted in 9.9%.⁶ In a smaller cohort of 153 patients with a

BAV with prior AVR, 3% required proximal aortic surgery after 15 years of follow-up. No cases of aortic dissection were noted.^{7,10} These studies demonstrate that the aorta may continue to dilate in patients with a BAV who undergo valve replacement surgery.¹¹

5.1.2. Interventions for Patients With BAV

5.1.2.1. Intervention: Replacement of the Aorta

Recommendations for Intervention: Replacement of the Aorta in Patients With a BAV		
Referenced studies that support the recommendations are summarized in Online Data Supplement 18.		
COR	LOE	Recommendations
1	B-NR	1. In asymptomatic or symptomatic patients with a BAV and a diameter of the aortic sinuses or ascending aorta >5.5 cm, operative intervention to replace the aortic sinuses and/or the ascending aorta is recommended. ^{1–3}
2a	B-NR	2. In asymptomatic patients with a BAV, a diameter of the aortic sinuses or ascending aorta of 5.0 to 5.5 cm, and an additional risk factor for dissection (eg, family history of aortic dissection, aortic growth rate >0.5 cm per year, aortic coarctation), operative intervention to replace the aortic sinuses and/or the ascending aorta is reasonable if the surgery is performed at a Comprehensive Valve Center. ^{3,4}

Recommendations for Intervention: Replacement of the Aorta in Patients With a BAV (Continued)		
COR	LOE	Recommendations
2a	B-NR	3. In patients with a BAV with indications for SAVR and a diameter of the aortic sinuses or ascending aorta ≥ 4.5 cm, replacement of the aortic sinuses and/or ascending aorta is reasonable if the surgery is performed at a Comprehensive Valve Center. ⁴⁻⁷
2b	C-LD	4. In patients with a BAV who meet criteria for replacement of the aortic sinuses, valve-sparing surgery may be considered if the surgery is performed at a Comprehensive Valve Center. ^{8,9}
2b	B-NR	5. In asymptomatic patients with a BAV who are at low surgical risk, have a diameter of the aortic sinuses or ascending aorta of 5.0 to 5.5 cm, and have no additional risk factors for dissection, operative intervention to replace the aortic sinuses and/or the ascending aorta may be considered if the surgery is performed at a Comprehensive Valve Center. ^{4-7,10-14}

Synopsis

The timing and type of surgery for replacement of the aorta are dependent on the anatomy of the aorta (as demonstrated on imaging), patient characteristics, and institutional expertise (Figure 6).

Recommendation-Specific Supportive Text

- Retrospective studies of patients with a BAV have shown that the incidence of aortic dissection is very low and is estimated to be approximately 0.4% with routine surveillance of the aorta.¹ However, data are limited with regard to the degree of aortic dilation at which the risk of dissection is high enough to warrant operative intervention in patients who do not fulfill criteria for AVR on the basis of severe AS or AR. Thus, an individualized approach to the timing of surgical intervention for a dilated aorta is suggested. Surgery is recommended in patients with a BAV with or without symptoms and with a diameter of the aortic sinuses or the ascending aorta of ≥ 5.5 cm.²
- Specific risk factors, including family history of aortic dissection, aortic growth rate >0.5 cm per year, and aortic coarctation, are associated with a greater risk of aortic dissection. In patients with these risk factors, operative intervention to replace the aortic sinuses and/or the ascending aorta is reasonable when the aortic dimension is 5.0 to 5.5 cm, if the surgery is performed at a Comprehensive Valve Center.^{4,10-12,15}
- In patients with a BAV, data are limited with regard to the degree of aortic dilation at which the risk of dissection is high enough to warrant replacement of the ascending aorta at the time of AVR. The risk of progressive aortic dilation and dissection after AVR in patients with BAV has been the subject of several studies, but definitive data are lacking. In

patients undergoing AVR because of severe AS or AR, replacement of the ascending aorta is reasonable when the aortic diameter is >4.5 cm.^{4-7,10-14}

- There are a limited number of patients with BAV who meet criteria for operative intervention on the aortic sinuses and/or ascending aorta but have a well-functioning aortic valve. Because of the growing experience with valve-sparing surgery on highly selected patients,^{8,9} surgical replacement of the aorta with aortic valve repair or reimplantation may be considered. However, given the complexity of this procedure, surgery should be performed at a Comprehensive Valve Center.
- Data are limited with regard to the degree of aortic dilation at which the risk of dissection is high enough to warrant operative intervention in patients who do not fulfill criteria for AVR on the basis of severe AS or AR. In asymptomatic patients with a BAV and a diameter of the aortic sinuses and/or ascending aorta of 5.0 to 5.5 cm who are at low surgical risk and have no additional risk factors for aortic dissection, surgery to replace the aortic sinuses and/or ascending aorta may be considered as long as surgery is performed at a Comprehensive Valve Center. Additionally, shared decision-making between the patient and the healthcare team is needed to clearly outline the risks of surgery and weigh them against the potential reduction in future risk of aortic dissection.^{4-7,10-14}

5.1.2.2. Intervention: Repair or Replacement of the Aortic Valve

Recommendations for Intervention: Repair or Replacement of the Aortic Valve		
Referenced studies that support the recommendations are summarized in Online Data Supplement 18.		
COR	LOE	Recommendations
2b	C-LD	1. In patients with BAV and severe AR who meet criteria for AVR, aortic valve repair may be considered in selected patients if the surgery is performed at a Comprehensive Valve Center. ¹⁻³
2b	B-NR	2. In patients with BAV and symptomatic, severe AS, TAVI may be considered as an alternative to SAVR after consideration of patient-specific procedural risks, values, trade-offs, and preferences, and when the surgery is performed at a Comprehensive Valve Center. ⁴⁻⁶

Synopsis

The indications for the timing of aortic valve intervention in patients with a BAV and AS or AR is similar to those for trileaflet aortic valves. See the respective sections on AS (Section 3.2) and AR (Section 4). The choice of prosthetic valve type in patients with a BAV is similar to that for patients with trileaflet valves. See the section on prosthetic valve choices (Section 3.2.4.1) for full details. Given the unique nature of BAV, however, there are additional specific considerations.

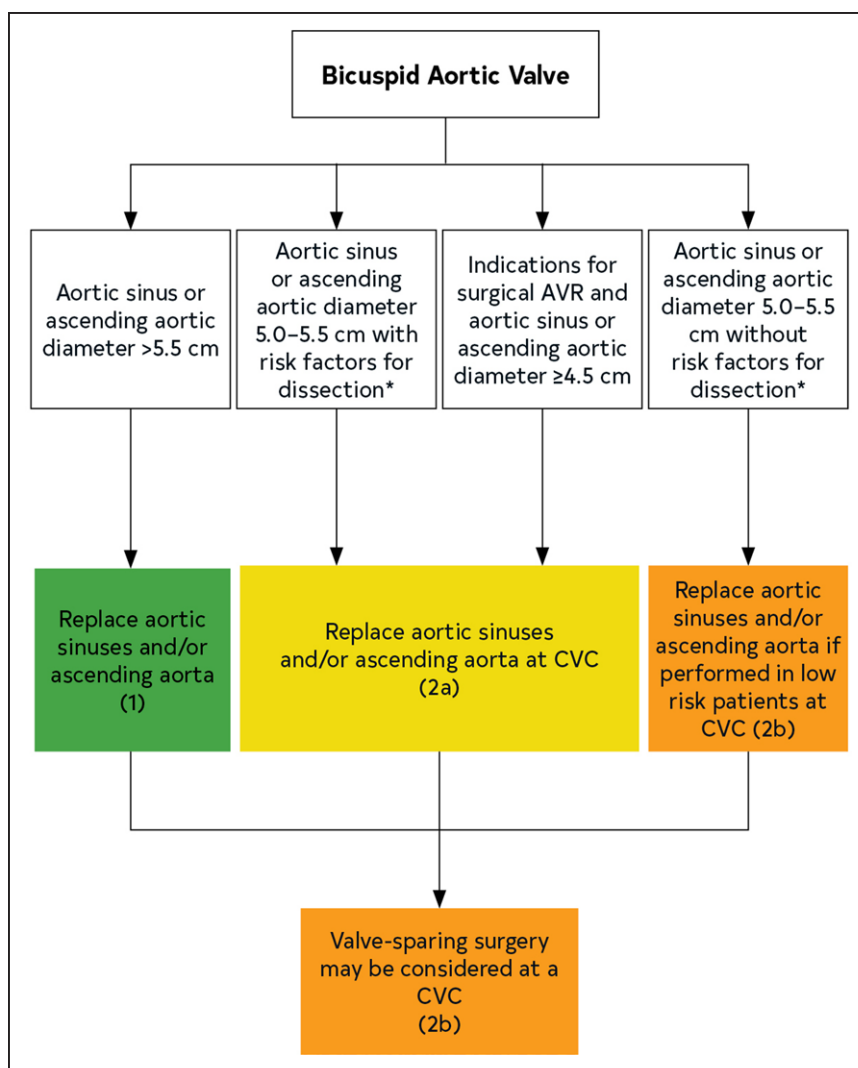


Figure 6. Intervention for replacement of the aorta in patients with a BAV.

Colors correspond to Table 2. *Family history of aortic dissection, aortic growth rate ≥ 0.5 cm/y, and/or presence of aortic coarctation. BAV indicates bicuspid aortic valve; AVR, aortic valve replacement; and CVC, Comprehensive Valve Center.

Recommendation-Specific Supportive Text

1. Surgical repair of the aortic valve may be feasible in selected patients, depending on valve and aortic root anatomy and tissue characteristics. Published data suggest that valve repair can be performed safely and effectively by surgeons with training and experience in these techniques.^{1–3,7} However, given the complexities of patient selection and surgical techniques, such surgeries should be performed at a Comprehensive Valve Center.
2. Recent trials have demonstrated the benefits of TAVI in patients with severe, symptomatic AS. However, the early pivotal TAVI trials excluded patients with BAV. Initial studies using early-generation valves suggested a higher rate of paravalvular leak in the BAV population.^{4,5} Data from the STS/ACC Transcatheter Valve Therapies Registry, which includes all consecutive TAVI procedures performed in the United States, suggest that with the use of newer-generation prosthetic valves the rate of paravalvular leak is no different in patients with a

BAV than in patients with a trileaflet aortic valve. This registry also showed no difference in mortality rate at 30 days and 1 year between the BAV and tricuspid valve groups. However, the stroke rate at 30 days was higher in the BAV group.⁶ Other considerations are the younger age of patients with a BAV, for whom the risk–benefit ratio of TAVI versus SAVR needs careful consideration. RCTs are needed to obtain full clarity on the optimal use of TAVI in this population, as well as long-term outcomes.

6. MITRAL STENOSIS

The incidence of rheumatic MS is low in high-income countries and has been slowly declining in low- and middle-income countries, but MS remains a major cause of valve disease worldwide. Rheumatic MS is much more common in women (about 80% of cases) than in men. The clinical presentation of rheumatic MS varies, with patients from regions with a high disease prevalence presenting at a young age (teen years to age 30 years)

Table 16. Stages of MS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered mitral valve area $>1.5 \text{ cm}^2$	Increased transmitral flow velocities Mitral valve area $>1.5 \text{ cm}^2$ Diastolic pressure half-time $<150 \text{ ms}$	Mild to moderate LA enlargement Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered mitral valve area $\leq 1.5 \text{ cm}^2$	Mitral valve area $\leq 1.5 \text{ cm}^2$ Diastolic pressure half-time $\geq 150 \text{ ms}$	Severe LA enlargement Elevated PASP $>50 \text{ mm Hg}$	None
D	Symptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered mitral valve area $\leq 1.5 \text{ cm}^2$	Mitral valve area $\leq 1.5 \text{ cm}^2$ Diastolic pressure half-time $\geq 150 \text{ ms}$	Severe LA enlargement Elevated PASP $>50 \text{ mm Hg}$	Decreased exercise tolerance Exertional dyspnea

The transmitral mean pressure gradient should be obtained to further determine the hemodynamic effect of the MS and is usually $>5 \text{ mm Hg}$ to 10 mm Hg in severe MS; however, because of 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; MS, mitral stenosis; and PASP, pulmonary artery systolic pressure.

with commissural fusion but pliable noncalcified valve leaflets. In contrast, the presentation in regions with a low disease prevalence occurs more often in older patients (age 50 to 70 years) who present decades after the initial rheumatic fever episode with calcified fibrotic leaflets in addition to commissural fusion and subvalvular involvement. Older patients with MS often have multiple other cardiac and noncardiac comorbidities, such as atherosclerotic disease, hypertension, and diastolic dysfunction, all of which need to be taken into consideration in patient evaluation and management.^{1,2}

Although most of MS in the world results from rheumatic heart disease, nonrheumatic calcific MS is found with increasing frequency in the elderly population in high-income countries. Calcific MS is the result of calcification of the mitral annulus that extends into the leaflet bases, resulting in both narrowing of the annulus and rigidity of the leaflets.^{3–5}

6.1. Stages of MS

The stages of MS are defined by patient symptoms, valve anatomy, valve hemodynamics, and the consequences of valve obstruction on the left atrium (LA) and pulmonary circulation (Table 16). Rheumatic valve disease is the primary cause of MS, with anatomic features reflecting this disease process. Hemodynamic severity is best characterized by valve area, either directly planimetered by 2D or 3D imaging or calculated from the diastolic pressure half-time.¹ The definition of “severe” MS is based on the severity of symptoms, 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, which typically corresponds to a transmitral mean gradient of

$>5 \text{ mmHg}$ to 10 mmHg at a normal heart rate. However, mean pressure gradient is highly dependent on transvalvular flow rate, the diastolic filling period, and heart rate. Mitral pressure half-time also has limitations, and is dependent upon LV and LA compliance as well as stenosis severity. Other approaches to calculation of the mitral valve area, such as the continuity equation or Gorlin formula, may be used if discrepancies exist. These pertain primarily to patients with rheumatic MS.

6.2. Rheumatic MS

6.2.1. Diagnosis and Follow-Up of Rheumatic MS

6.2.1.1. Diagnostic Testing: Initial Diagnosis

Recommendations for Diagnostic Testing: Initial Diagnosis of Rheumatic MS		
Referenced studies that support the recommendations are summarized in Online Data Supplement 19.		
COR	LOE	Recommendations
1	B-NR	1. In patients with signs or symptoms of rheumatic MS, TTE is indicated to establish the diagnosis, quantify hemodynamic severity, assess concomitant valvular lesions, and demonstrate valve morphology (to determine suitability for mitral commissurotomy). ^{1–3}
1	C-LD	2. In patients considered for percutaneous mitral balloon commissurotomy (PMBC), TEE should be performed to assess the presence or absence of LA thrombus and to evaluate the severity of MR. ^{4–6}

Synopsis

For patients with rheumatic MS, TTE is the initial diagnostic test to determine the severity of the stenosis

and suitability for PMBC. If PMBC is being considered, a TEE can further evaluate the presence and severity of concomitant MR and rule out LA thrombus.

Recommendation-Specific Supportive Text

1. TTE is the imaging modality of choice to elucidate the anatomy and functional significance of rheumatic MS.¹ The parasternal long-axis window can identify the characteristic diastolic doming of the mitral valve, whereas short-axis scanning will demonstrate commissural fusion and allow planimetry of the mitral orifice. Use of 3D echocardiography (either TTE or TEE) provides greater accuracy of measurement of the mitral valve area.^{7,8} Doppler echocardiography mean transvalvular gradients always should be reported with heart rate because a high heart rate will result in overestimation of stenosis severity.⁹ Estimated RV systolic pressure is obtained from the TR velocity. Concomitant MR should be quantified, along with any other valve lesions (Section 7.3.1.1). Several scores are available for evaluation of mitral valve morphology and prediction of outcomes with PMBC, and these scores consider valve thickening, mobility, and calcification with subvalvular chordal fusion.^{10,11} Characterization of commissural morphology and calcification further predicts suitability for commissurotomy.^{2,3,12,13} Additional assessment of rheumatic MS includes the mitral pressure half-time, with acknowledgment that this parameter is also affected by LA and LV compliance. If the mean gradient does not match the valve area, other methods, such as the continuity equation, should be considered.¹⁴
2. TEE offers excellent visualization of the mitral valve and LA and is an alternative approach to assessment of rheumatic MS in patients whose TTE images are technically limited. In patients being considered for PMBC, a TEE can rule out LA cavity and appendage thrombi.⁴⁻⁶ TEE also is useful for evaluation of MR severity in patients being considered for PMBC because shadowing of the LA on TTE may result in underestimation of MR severity. MR that is more than mild is a contraindication to PMBC.

6.2.1.2. Diagnostic Testing: Changing Signs or Symptoms

Patients with an established diagnosis of rheumatic MS may experience a change in symptoms attributable to disease progression related to recurrent episodes of rheumatic fever leading to further valve damage; progressive narrowing of the mitral valve attributable to leaflet fibrosis and thickening; progressive pulmonary hypertension;

or worsening of concomitant MR or other valve lesions. In addition, symptom status may change with no change in rheumatic MS severity because of an increased hemodynamic load (for example, because of pregnancy), new-onset or rapid AF, fever, anemia, or hyperthyroidism, or hemodynamic shifts in the perioperative period of patients undergoing noncardiac surgery. In such cases, a repeat TTE examination can quantify the mitral valve gradient and area, as well as other parameters that may contribute to a change in symptoms.

6.2.1.3. Diagnostic Testing: Routine Follow-Up

Rheumatic MS is a slowly progressive disease, characterized by a prolonged latent phase between the initial rheumatic illness and the development of valve stenosis.¹⁻³ The latent phase is an interval typically measured in decades in high-income countries but in considerably shorter periods in low- to middle-income countries, likely because of recurrent carditis. Once mild stenosis has developed, further narrowing is slow (decrease in valve area of 0.1 cm² per year on average), although the rate of progression is highly variable.³ Importantly, progressive enlargement of the RV and a rise in RV systolic pressure can be observed, even in the absence of a decrease in mitral valve area. Accordingly, repeat TTE at intervals dictated by valve area is an important aspect of disease management, even in patients without symptoms (Table 4).

6.2.1.4. Diagnostic Testing: Cardiac Catheterization

In the contemporary era, assessment of MS and associated lesions can be obtained in most patients by TTE, occasionally supplemented by TEE. However, there will be a subset of patients with nondiagnostic studies or for whom there is discordance between the clinical and echocardiographic findings. In older patients, other factors contributing to symptoms may need to be further sorted out, such as concomitant diastolic dysfunction, LA noncompliance, or intrinsic pulmonary vascular disease. Cardiac catheterization is useful in these patients to further characterize rheumatic MS hemodynamics and etiology of symptoms, as it can measure absolute pressures in the LV, LA, and pulmonary circulation at rest and with exercise. Although the mean pulmonary artery wedge pressure is an acceptable substitute for mean LA pressure, the LV-to-pulmonary wedge gradient will overestimate the true transmitral gradient because of phase delay and delayed transmission of pressure changes.¹ Nonetheless, the absolute mean pulmonary artery wedge pressure and its relationship to the LV diastolic pressure and pulmonary artery pressure can provide useful clinical information. The Gorlin equation can be used for an independent calculation of mitral valve area.^{2,3}

6.2.1.5. Diagnostic Testing: Exercise Testing

Recommendation for Diagnostic Testing: Exercise Testing in Patients With Rheumatic MS		
COR	LOE	Recommendation
1	C-LD	1. In patients with rheumatic MS and a discrepancy between resting echocardiographic findings and clinical symptoms, exercise testing with Doppler or invasive hemodynamic assessment is recommended to evaluate symptomatic response, exercise capacity, and the response of the mean mitral gradient and pulmonary artery pressure. ¹⁻⁵

Synopsis

Exercise testing with either Doppler echocardiography or cardiac catheterization is important when the resting hemodynamics do not match the clinical symptoms in patients with rheumatic MS.

Recommendation-Specific Supportive Text

- Exercise testing with hemodynamics is helpful in the management of rheumatic MS when a patient's symptoms seem significantly greater than or less than would be expected from TTE. Results have been published in which both exercise and dobutamine were used with Doppler echocardiography, although exercise is preferred in general as the more physiological test.¹⁻⁶ Most experience is with treadmill exercise, with images and Doppler obtained immediately after stress, but bicycle exercise allows data acquisition at various stages of exercise. Bicycle exercise testing during cardiac catheterization can also be performed for direct measurements of pulmonary artery wedge pressure and pulmonary pressures at rest and with exercise. Simple functional capacity helps to quantify the patient's symptoms. Changes in valve gradient should be measured, as well as the estimated pulmonary artery systolic pressure. If the patient cannot exercise, increasing the heart rate with maneuvers such as leg lifts or sit-ups may be useful.

6.2.2. Medical Therapy

Recommendations for Medical Therapy in Patients With Rheumatic MS Referenced studies that support the recommendations are summarized in Online Data Supplement 30.		
COR	LOE	Recommendations
1	C-LD	1. In patients with rheumatic MS and 1) AF, 2) a prior embolic event, or 3) an LA thrombus, anticoagulation with a VKA is indicated. ¹⁻⁷
2a	C-LD	2. In patients with rheumatic MS and AF with a rapid ventricular response, heart rate control can be beneficial. ⁸
2a	A	3. In patients with rheumatic MS in normal sinus rhythm with symptomatic resting or exertional sinus tachycardia, heart rate control can be beneficial to manage symptoms. ⁹⁻¹⁵

Synopsis

In patients with rheumatic MS and AF, anticoagulation decreases the incidence of thromboembolic events. Anticoagulation can also decrease the incidence of thromboembolic events in patients with rheumatic MS if there has been a prior embolic event or if an LA thrombus was visualized. In symptomatic patients with MS who are in normal sinus rhythm and have tachycardia, heart rate control with beta blockers, calcium channel blockers, or ivabradine will lengthen the diastolic filling period and lower LA pressure. However, routine use of heart rate control for patients with rheumatic MS in normal sinus rhythm in the absence of tachycardia may result in chronotropic incompetence, preventing an adequate cardiac output response to exercise.

Recommendation-Specific Supportive Text

- Patients with rheumatic MS with AF and prior embolic events are at high risk of arterial embolization when AF or an LA thrombus is present. Treatment with VKA anticoagulation will decrease the incidence of these events.^{3-7,16} It is controversial whether long-term anticoagulation should be given to patients with rheumatic MS in normal sinus rhythm on the basis of LA enlargement or spontaneous contrast on TEE.^{17,18} Patients with very large left atria have more spontaneous echocardiographic contrast and lower LA appendage Doppler velocities,¹⁹ which have been associated with a higher rate of embolic events, but no data directly link large left atria to embolic events. Non-vitamin K oral anticoagulation has not been studied in patients with rheumatic MS, and these patients were excluded from the randomized AF trials. In addition to the much higher risk of embolization with rheumatic valve disease as compared with other causes of valve disease, there is concern that rheumatic disease also affects the atrial muscle, resulting in an increased risk of blood flow stasis and thrombosis in the body of the LA, as well as the LA appendage.¹ Further studies are required to confirm these findings.²
- Patients with rheumatic MS are prone to developing atrial arrhythmias—specifically AF. Significant detrimental hemodynamic consequences may be associated with the acute development of AF, primarily from the rapid ventricular response, which shortens the diastolic filling period and increases LA pressure.¹⁶ The treatment of acute AF consists of anticoagulation and control of the heart rate response with negative dromotropic agents. If the rate cannot be adequately controlled with medications, cardioversion may be necessary to improve hemodynamics. In the stable patient, the decision

for rate control versus rhythm control is dependent on multiple factors, including the duration of AF, hemodynamic response to AF, LA size, prior episodes of AF, and history of embolic events. It is more difficult to achieve rhythm control in patients with rheumatic MS because the rheumatic process itself may lead to progressive fibrosis and enlargement of the atria, fibrosis of the internodal and interatrial tracts, and damage to the sinoatrial node.

3. The use of negative dromotropic agents for the treatment of symptoms in patients with rheumatic MS in normal sinus rhythm has been controversial. Although a reduction in heart rate and prolongation of the diastolic filling period will decrease the transmitral mean gradient, studies have shown that treatment with beta blockade may not improve or may even decrease exercise tolerance, most likely because of the limitation of the cardiac output attributable to a limited stroke volume and chronotropic incompetence.^{9–11} Nonetheless, there are now several randomized trials that have examined beta blockers and ivabradine in patients with rheumatic MS and have shown that either drug can increase exercise duration and improve symptoms.^{2–15} To explain these differences, the earlier trials that found no benefit of beta blockers were performed in older patients with underlying chronotropic incompetence, whereas the randomized trials showing benefit were performed primarily in younger patients with higher resting and exercise-induced heart rates. Thus, the use of beta blockers or ivabradine to improve symptoms may be effective only in patients who do not have underlying chronotropic incompetence. When medical therapy is considered for relief of symptoms in patients with rheumatic MS, it must be remembered that intervention with PMBC relieves symptoms in those patients with an appropriate valve morphology.

6.2.3. Intervention

Recommendations for Intervention for Rheumatic MS Referenced studies that support the recommendations are summarized in Online Data Supplements 21 to 24.		
COR	LOE	Recommendations
1	A	1. In symptomatic patients (NYHA class II, III, or IV) with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage D) and favorable valve morphology with less than moderate (2+) MR* in the absence of LA thrombus, PMBC is recommended if it can be performed at a Comprehensive Valve Center. ^{1–12}
1	B-NR	2. In severely symptomatic patients (NYHA class III or IV) with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage D) who 1) are not candidates for PMBC, 2) have failed a previous PMBC, 3) require other cardiac procedures, or 4) do not have access to PMBC, mitral valve surgery (repair, commissurotomy, or valve replacement) is indicated. ^{6,7,13}

Recommendations for Intervention for Rheumatic MS (Continued)		
COR	LOE	Recommendations
2a	B-NR	3. In asymptomatic patients with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage C) and favorable valve morphology with less than 2+ MR in the absence of LA thrombus who have elevated pulmonary pressures (pulmonary artery systolic pressure >50 mmHg), PMBC is reasonable if it can be performed at a Comprehensive Valve Center. ¹⁴
2b	C-LD	4. In asymptomatic patients with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage C) and favorable valve morphology with less than 2+ MR* in the absence of LA thrombus who have new onset of AF, PMBC may be considered if it can be performed at a Comprehensive Valve Center. ¹⁵
2b	C-LD	5. In symptomatic patients (NYHA class II, III, or IV) with rheumatic MS and an mitral valve area >1.5 cm ² , if there is evidence of hemodynamically significant rheumatic MS on the basis of a pulmonary artery wedge pressure >25 mmHg or a mean mitral valve gradient >15 mmHg during exercise, PMBC may be considered if it can be performed at a Comprehensive Valve Center. ¹⁶
2b	B-NR	6. In severely symptomatic patients (NYHA class III or IV) with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage D) who have a suboptimal valve anatomy and who are not candidates for surgery or are at high risk for surgery, PMBC may be considered if it can be performed at a Comprehensive Valve Center. ^{17–19}

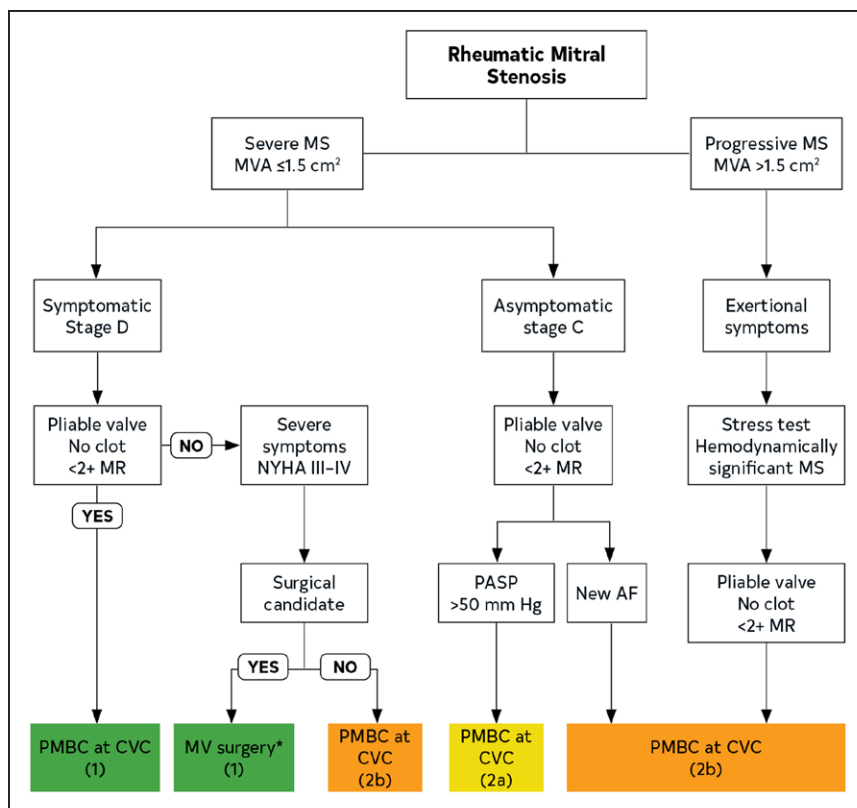
*2+ on a 0 to 4+ scale according to Sellar's criteria or less than moderate by Doppler echocardiography.²⁰

Synopsis

The optimal treatment of patients with rheumatic MS is either PMBC or surgery (open or closed commissurotomy). Although these procedures can result in excellent outcomes by splitting open fused commissures to relieve stenosis, both the catheter-based and the surgical procedures require a high level of expertise and should be performed at experienced centers. In the United States, there has been a 7.5% decrease in the use of PMBC, accompanied by a 15.9% increase in complication rate.²¹ Excellent short- and long-term outcomes can be achieved with surgical commissurotomy, but surgical commissurotomy is not routinely or widely performed by most surgeons in the United States. Thus, in the clinical decision-making process for a patient with rheumatic MS, it is essential to know the results of the available interventional procedures. Mitral valve replacement is an option for treatment only if there is no other option and the patient has severe limiting symptoms (Figure 7).

Recommendation-Specific Supportive Text

1. Randomized trials have established the safety and efficacy of PMBC as compared with surgical closed or open commissurotomy in patients with a

**Figure 7. Intervention for MS.**

Colors correspond to Table 2. *Repair, commissurotomy, or valve replacement. AF indicates atrial fibrillation; CVC, Comprehensive Valve Center; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; and PMBC, percutaneous mitral balloon commissurotomy.

favorable valve morphology with less than 2+ MR in the absence of LA thrombus.^{6,8–12} PMBC is performed by advancing one or more balloon catheters across the mitral valve and inflating them, thereby splitting the commissures. Favorable valve morphology consists of mobile and relatively thin valve leaflets, which are free of calcium, in the absence of significant subvalvular fusion.^{18,19,22,23} An anatomic mitral morphology score can be used to determine suitability for PMBC and to evaluate the appearance of the commissures and degree of calcification.^{1,24,25} Clinical factors, such as age, NYHA class, and presence or absence of AF, are also predictive of outcome. Older patients with lower gradients (<10 mm Hg) will not have as good an outcome as patients with higher gradients, probably because of other concomitant problems that cause symptoms, such as LV diastolic dysfunction and LA noncompliance, measured by net atrial-ventricular compliance.^{26–30} PMBC should be performed only by experienced operators, with immediate availability of surgical backup for potential complications. Long-term follow-up has shown 70% to 80% of patients with an initial good result after PMBC to be free of recurrent symptoms at 10 years, and 30% to 40% are free of recurrent symptoms at 20 years.^{1–7}

2. Mitral valve surgery is an established therapy for rheumatic MS, with the preferred approach being commissurotomy (either closed, where the valve is

opened blindly through the LA or LV, or open, which allows more extensive surgery under direct visualization) when anatomy is favorable.^{31–36} However, in the presence of severe valvular thickening and subvalvular fibrosis with leaflet tethering, mitral valve replacement may be the best option. In addition to those who have suboptimal valve anatomy (or failed PMBC), patients with moderate or severe TR may also have a better outcome with a surgical approach that includes tricuspid valve repair.³⁷ Patients undergoing surgical commissurotomy at centers with a high level of expertise may have better long-term outcomes than those undergoing PMBC.^{6,7} Because the natural history of rheumatic MS is one of slow progression over decades, surgery should be delayed until the patient has severe limiting symptoms (NYHA class III or IV), particularly if mitral valve repair is contemplated.

3. Although most patients with rheumatic MS who are asymptomatic will do well for years without intervention, an elevation of pulmonary artery pressure is an indication that there is progressive elevation of LA pressure affecting the pulmonary circulation. An elevated pulmonary pressure can be assessed by Doppler echocardiography. Although there may be a decrease in pulmonary pressure after relief of the rheumatic MS,³⁸ some patients will have developed intrinsic pulmonary vascular disease, as evidenced by a poorer long-term survival rate in patients who have pulmonary hypertension before

intervention.^{14,39} An elevated pulmonary arterial resistance before intervention is associated with RV dysfunction and TR after the procedure.^{40–42} Thus, PMBC may prevent the adverse consequences of irreversible pulmonary hypertension if it can be performed with a high success rate and low risk in patients who are developing pulmonary hypertension. Correction of the MR before irreversible changes occur can be curative. Thus, in chronic primary MR, MR is the disease.

4. The new onset of AF may be an indication for proceeding with PMBC in the asymptomatic patient with a favorable valve morphology for several reasons. First, AF may be the equivalent of symptom onset, signifying that rheumatic MS is resulting in progressive LA damage. Second, AF increases the risk of thromboembolic events in patients with rheumatic MS. In addition, a shortened diastolic filling interval with AF and a rapid ventricular response further increase LV pressure. Finally, the presence of AF is associated with worse outcomes in patients with rheumatic MS and with suboptimal results after PMBC.⁴³ In theory, lowering a high LA pressure after PMBC might be beneficial in restoring normal sinus rhythm. Although there is no randomized trial to prove the effectiveness of intervening early, there is a documented improvement in P-wave dispersion after PMBC, which may affect the ability to restore normal sinus rhythm.¹⁵
5. Some patients have symptoms from rheumatic MS even with a mitral valve area >1.5 cm² and a resting mean transmitral gradient <10 mmHg. This may be related to the variability and reliability of measuring a mitral valve area by either planimetry of a short-axis image of the mitral valve or using a diastolic half-time for indirect calculation of the mitral valve area. There are also patients who have a relatively low gradient at rest who generate a much higher gradient with exercise, with symptoms developing from the higher LA pressure. Thus, in these patients in whom there is a discrepancy between the clinical symptoms and the resting hemodynamics, exercise testing with measurement of the mean transmitral gradient or the direct pulmonary artery wedge, or both, is useful.^{44–48} Patients who increase their gradients to >15 mmHg with exercise have been shown to improve symptomatically after PMBC.¹⁶
6. Both anatomic valve morphology and the presence of commissural calcification predict successful PMBC. However, in all such series, this predictive ability is not absolute, with 42% of patients with an anatomic valve Wilkins morphology score >8 ^{22,23,31,32} having an optimal outcome (25% increase in mitral valve area to >1.5 cm²) and 38% of patients with commissural calcium having

event-free survival at 1.8 years.^{18,19,22,23} Accordingly, severely symptomatic patients who are poor surgical candidates may benefit from PMBC even with suboptimal valve anatomy.¹⁷ Patients who refuse surgery may also be offered PMBC after discussion about the potential complications associated with this procedure when it is performed in patients with suboptimal valve anatomy.

6.3. Nonrheumatic Calcific MS

Recommendation for Nonrheumatic Calcific MS		
COR	LOE	Recommendation
2b	C-LD	1. In severely symptomatic patients (NYHA class III or IV) with severe MS (mitral valve area ≤ 1.5 cm ² , Stage D) attributable to extensive mitral annular calcification, valve intervention may be considered only after discussion of the high procedural risk and the individual patient's preferences and values. ^{1–3}

Synopsis

Although most MS in the world results from rheumatic heart disease, calcific MS is found with increasing frequency in the elderly population in high-income countries.^{2–10} Calcific MS is the result of calcification of the mitral annulus that extends into the leaflet bases, resulting both in narrowing of the annulus and rigidity of the leaflets. In contrast to rheumatic MS, there is no commissural fusion, and the leaflet tips are usually unaffected. The progression of calcific MS is variable, ranging from an increase of <1.0 to up to 9 mmHg per year.^{9,11} The prognosis of this group of patients is poor, with a 5-year survival rate $<50\%$, most likely because of advanced age and other comorbidities.⁴ Determination of the severity of stenosis is difficult because of extensive calcification, which prevents measurement of an accurate planimetered area, and the significant abnormalities of LA and LV compliance, which cause a high gradient in the absence of severe obstruction.^{12–16} These patients are at high risk with any intervention because of the extensive calcification, as well as advanced age and multiple comorbidities. Thus, in patients with calcific MS, the indications for any intervention differ from those for rheumatic MS, and intervention for calcific MS should be performed only in the highly symptomatic patient. Nonrheumatic MS can also be present after radiation therapy and after a mitral valve repair with a small annuloplasty ring.

Recommendation-Specific Supportive Text

1. Indications for intervention in patients with calcific MS are different from those for rheumatic MS for the following reasons. First, because calcification involves the annulus and base of the leaflets without commissural fusion, there is no role

for PMBC or surgical commissurotomy. Second, the presence of severe mitral annular calcification can be quite challenging for the surgeon because of technical difficulty in securely attaching the prosthetic valve and placement of the prosthetic valve may result in narrowing of the orifice.^{17–22} Finally, patients with calcification are often elderly and debilitated, have multiple comorbidities, and are at high surgical risk.^{1–3} For these reasons, intervention should be delayed until symptoms are severely limiting and cannot be managed with diuresis and heart rate control. Catheter-based therapies for these high-surgical risk patients are being developed and evaluated.²³

7. MITRAL REGURGITATION

7.1. Acute MR

Acute MR may be caused by disruption of different parts of the mitral valve apparatus. IE may cause leaflet perforation or chordal rupture. Spontaneous chordal rupture may occur in patients with myxomatous mitral valve disease. Rupture of the papillary muscle occurs in patients who have an acute ST-segment-elevation myocardial infarction, usually associated with an inferior infarction. The acute volume overload on the LV and LA results in pulmonary congestion and low forward cardiac output.^{1–4} Diagnosis of the presence and etiology of acute MR, along with urgent intervention, may be lifesaving.

7.1.1. Diagnosis of Acute MR

In patients with acute MR, TTE is the initial imaging modality of choice to evaluate LV function, RV function, pulmonary artery pressure, and mechanism of MR. The patient with severe acute MR, which might occur from chordal rupture, usually experiences acute hemodynamic decompensation. The sudden volume overload increases LA and pulmonary venous pressures, leading to pulmonary congestion and hypoxia, whereas decreased blood delivery to the tissues with a concomitant decrease in LV systolic pressure limits the pressure gradient, driving MR to early systole. Thus, the murmur may be short and unimpressive, as may be the color jet of MR by TTE. In the presence of sudden acute and hemodynamic instability after myocardial infarction, with hyperdynamic LV function by TTE and no other cause for the deterioration, TEE can be especially helpful in detecting papillary muscle or chordal rupture or valvular vegetations and annular abscesses that may further accentuate the need for a more urgent surgical approach.¹

7.1.2. Medical Therapy

Vasodilator therapy improves hemodynamic compensation in acute MR. The premise for use of vasodilators in acute MR is a reduction in impedance of aortic flow, thereby preferentially guiding flow away from the

LV-to-LA pathway, decreasing MR while simultaneously increasing forward output to the LV-to-aortic pathway.^{1,2} This is usually accomplished by infusion of an easily titratable agent, such as sodium nitroprusside or nicardipine. Use of vasodilators is often limited by systemic hypotension that is exacerbated when peripheral resistance is decreased. Intra-aortic balloon counterpulsation can be helpful to treat acute severe MR. By lowering systolic aortic pressure, intra-aortic balloon counterpulsation decreases LV afterload, increasing forward output while decreasing regurgitant volume. Simultaneously, intra-aortic balloon counterpulsation increases diastolic and mean aortic pressures, thereby supporting the systemic circulation. The use of a percutaneous circulatory assist device may stabilize a patient with acute hemodynamic compromise before the procedure.

7.1.3. Intervention

Prompt mitral valve surgery, preferably mitral repair if possible, is lifesaving in the symptomatic patient with acute severe primary MR. The severity of acute primary MR is variable, and some patients with more moderate amounts of MR may develop compensation as LV dilation allows for lower filling pressure and increased forward cardiac output. However, most patients with acute severe MR require surgical correction for reestablishment of normal hemodynamics and for relief of symptoms.^{1–5} This is especially true for a complete papillary muscle rupture that causes very severe MR, which is poorly tolerated.

7.2. Chronic Primary MR

7.2.1. Stages of Chronic Primary MR

In assessing the patient with chronic MR, it is important to distinguish between chronic *primary* (degenerative) MR and chronic *secondary* (functional) MR, as these 2 conditions have more differences than similarities. Primary MR is a disease of the mitral valve apparatus, and secondary MR is a disease of the ventricle or atria. 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 LV to the LA (Table 17). The most common cause of chronic primary MR in high-income 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). A subset of these patients will present with ventricular arrhythmias, mitral annular disjunction, and LV dilation. Alternatively, older populations present with fibroelastic deficiency disease, in which lack of connective tissue leads to chordal rupture. The differentiation between these 2 etiologies may have 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 volume overload of chronic primary MR is prolonged and severe, it causes myocardial damage, HF, and eventual death. Correction of the MR before irreversible changes occur can be curative.

7.2.2. Diagnosis and Follow-Up of Chronic Primary MR

7.2.2.1. Diagnostic Testing: Initial Diagnosis

Recommendations for Diagnostic Testing: Initial Diagnosis of Chronic MR		
Referenced studies that support the recommendations are summarized in Online Data Supplement 25.		
COR	LOE	Recommendations
1	B-NR	1. In patients with known or suspected primary MR, TTE is indicated for baseline evaluation of LV size and function, RV function, LA size, pulmonary artery pressure, and the mechanism and severity of primary MR (Stages A to D). ¹⁻⁵
1	C-EO	2. In patients with primary MR, when TTE provides insufficient or discordant information, TEE is indicated for evaluation of the severity of MR, mechanism of MR, and status of LV function (Stages B to D).
1	B-NR	3. In patients with primary MR, CMR is indicated to assess LV and RV volumes and function and may help with assessing MR severity when there is a discrepancy between the findings on clinical assessment and echocardiography. ⁶⁻⁹
1	B-NR	4. In patients with severe primary MR undergoing mitral intervention, intraoperative TEE is indicated to establish the anatomic basis for primary MR (Stages C and D) and to guide repair. ^{10,11}

Synopsis

TTE is the initial imaging modality for patients with primary MR to look at valve morphology, severity of the MR, and the status of the LV, with TEE, CMR, or cardiac catheterization performed when insufficient or discordant information is obtained from the TTE. A TEE should be used to guide mitral valve interventions.

Recommendation-Specific Supportive Text

1. TTE images provide the diagnostic data needed for clinical decision-making in chronic primary MR.^{1-5,12} The outcome of the patient with chronic primary MR is determined by lesion severity,⁵ symptomatic status.¹³⁻¹⁵ the presence of LV dysfunction, and whether valve pathology is correctable by valve repair, which is superior to valve replacement when repair is possible. Usually only severe (not mild or moderate) MR leads to negative sequelae.^{5,6} Favorable loading conditions in MR increase LVEF but do not affect the extent of shortening. Thus, a "normal" LVEF in MR is

approximately 70%. The onset of LV dysfunction is inferred when LVEF declines toward 60% or when the LV is unable to contract to a diameter <40 mm at end systole.¹⁶⁻¹⁸ Although chamber volumes may give more information about cardiac remodeling,¹⁹ 2D volume accuracy is variable in clinical practice. Determination of MR severity is made by integrating all available data. These data include measurements of the effective orifice area, regurgitant volume, regurgitant fraction (obtained by using the proximal isovelocity surface area or quantitative Doppler flow measurements),^{1-3,5,20} color jet area, vena contracta, continuous-wave Doppler intensity, and the transmitral jet velocity curve. In mitral valve prolapse, MR may be non-holosystolic (mid-late systole). Thus, careful attention in assessing its severity is needed as conventional color Doppler parameter may overestimate its severity on a single image frame. Volumetric measurements provide a better assessment in this situation.⁹

2. TEE provides excellent imaging of the mitral valve and should be performed when TTE images are inadequate to fulfill the goals of TTE noted previously. TEE is especially useful in cases of MR attributable to IE because TEE can provide information about other potentially infected structures. TEE may allow more precise quantitation of regurgitant severity and provide a better estimate of the likelihood of a successful surgical valve repair than does TTE. Three-dimensional TEE may be helpful in further visualizing the abnormal mitral valve anatomy, offering a "surgical" view of the valve. Mitral valve repair is preferable to valve replacement because of a lower operative mortality rate and avoidance of the complications inherent to prosthetic valves. Although the final decision about repair versus replacement is made in the operating room, TEE can help predict surgical strategy beforehand. Thus, if repair is likely, it might be performed earlier in the course of the disease than if replacement is necessary.
3. In most cases, TTE provides the data needed for adequate cardiac evaluation of the patient with MR. However, in cases where TTE image quality is poor, CMR may be of value in MR evaluation. CMR produces highly accurate data on LV volumes, RV volumes, and LVEF, as well as an assessment of regurgitant fraction for estimating MR severity.⁶⁻⁹ However, outcome data on large numbers of patients have been derived from echocardiography, and it is uncertain whether CMR data can be used interchangeably with echocardiographic data in predicting outcomes. CMR is less helpful in establishing mitral pathoanatomy.

Table 17. Stages of Chronic Primary MR

Stage	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	At risk of MR	Mild mitral valve prolapse with normal coaptation Mild valve thickening and leaflet restriction	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	Progressive MR	Moderate to severe mitral valve prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE	Central jet MR 20%–40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm Regurgitant volume <60 mL Regurgitant fraction <50% ERO <0.40 cm ² Angiographic grade 1+ to 2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	Asymptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm ² Angiographic grade 3+ to 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/or LVESD ≥40 mm	None
D	Symptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm ² Angiographic grade 3+ to 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.

4. Intraoperative TEE is the standard for imaging during MR surgery. Before the operative incision, TEE may give the surgeon a better understanding of the valve anatomy and type of repair that will likely be performed, although this decision is ultimately made when the valve is inspected visually.^{10,11} Three-dimensional TEE ("surgical view") may be helpful in further visualizing the abnormal mitral valve anatomy. Because anesthesia lessens afterload, preload, and mitral valve closing force, decisions about severity of MR should be evaluated at the same loading conditions as occurred during the awake state. Intraoperative TEE is especially helpful in gauging the adequacy of repair.¹¹ Because even mild residual MR after repair increases the likelihood of later repair failure that would necessitate reoperation,²¹ surgeons strive for near-perfect operative repair. Adequacy of repair is judged by TEE after physiological filling pressure and blood pressure have been established. If more than trivial MR is detected in the operating room after repair, repair revision usually ensues. TEE also helps to

diagnose underfilling of the LV, which can lead to systolic anterior leaflet motion with outflow obstruction and unneeded repair. In those patients with primary severe MR who are at high surgical risk, TEE is helpful in determining the feasibility of transcatheter edge-to-edge repair.^{22,23}

7.2.2.2. Diagnostic Testing: Changing Signs or Symptoms

Recommendation for Diagnostic Testing: Changing Signs or Symptoms in Patients With Primary MR

Referenced studies that support the recommendation are summarized in Online Data Supplement 28.

COR	LOE	Recommendation
1	B-NR	1. In patients with primary MR (Stages B to D) and new-onset or changing symptoms, TTE is indicated to evaluate the mitral valve apparatus and LV function. ^{1,2}

Synopsis

A repeat TTE provides clinically relevant information about patients who are being followed for primary MR who develop new-onset symptoms.

Recommendation-Specific Supportive Text

1. The onset of symptoms in severe MR (dyspnea on exertion, orthopnea, or declining exercise tolerance) is an indication for mitral intervention even if LV function is preserved.² Symptoms are the culmination of the pathophysiology of MR and may indicate changes in LV or LA compliance; increase in pulmonary artery pressure; decrease in RV function; or the coexistence of TR. Therefore, symptoms add pathophysiological data not readily available from imaging, if other confounding factors can be excluded. Furthermore, there is no evidence that treatment with diuretics or other therapies that might relieve symptoms changes the prognostic effect of symptom onset. Once symptoms have occurred and are caused by MR, mitral valve surgery will improve the natural history even if medication has led to improvement. Repeat TTE at the time of symptom onset is indicated to confirm that symptoms are likely attributable to MR or its effect on the LV, which in turn supports surgical correction.¹ The new onset of AF is also an indication for repeat TTE to look for changes in severity of MR and the status of the LV.

7.2.2.3. Diagnostic Testing: Routine Follow-Up

Recommendations for Diagnostic Testing: Routine Follow-Up for Chronic Primary MR		
Referenced studies that support the recommendations are summarized in Online Data Supplement 27.		
COR	LOE	Recommendations
1	B-NR	1. For asymptomatic patients with severe primary MR (Stages B and C1), TTE is indicated every 6 to 12 months for surveillance of LV function (estimated by LVEF, LVEDD, and LVESD) and assessment of pulmonary artery pressure. ¹⁻¹¹
2b	B-NR	2. In asymptomatic patients with severe primary MR (Stages B and C1), use of serum biomarkers and novel measurements of LV function, such as global longitudinal strain, may be considered as an adjunct to guide timing of intervention. ¹²⁻²¹

Synopsis

Asymptomatic patients with severe primary MR require periodic TTE to determine optimal timing of intervention. Biomarkers and other measures of LV function, such as global longitudinal strain, may also be helpful to guide intervention.

Recommendation-Specific Supportive Text

1. TTE provides valuable information for surveillance of LV function (estimated by LVEF and LVESD) and pulmonary artery pressure in asymptomatic patients with severe primary MR (Stage C1) if performed every 6 to 12 months.^{1,2,4,5,7-11} Chronic severe MR is tolerated poorly, reaching a trigger

for surgery at an average rate of about 8% per year.^{5,10} This progression varies from patient to patient, and because prognosis worsens if correction of MR is delayed beyond the onset of these triggers, referral to a Comprehensive Valve Center for early repair or careful surveillance is of value. Because echocardiographic measurements are variable, management decisions that rest on these measurements should be confirmed by repeat sequential TTE. In patients with milder chronic primary MR (Stages A and B), TTE is indicated periodically to evaluate for changes in MR severity, depending on valve anatomy and other considerations, because regurgitation may worsen over time. Because this process may develop slowly, MR can become severe and even lead to LV dysfunction in the absence of symptoms or clinical signs (Table 4).^{3,6}

2. Symptom onset is a crucial demarcation point in the natural history of MR and also a trigger for intervention. Because symptoms develop gradually, patients may fail to recognize or ignore symptoms. Natriuretic peptide levels provide objective evidence in patients with chronic severe MR, with elevated levels indicating increased reliance on preload to maintain an adequate forward cardiac output.^{12-18,20} Thus, serum natriuretic peptide levels may be helpful in making management decisions about intervention when other data are conflicting. LVEF is used as a key determinant of LV function in timing MR intervention. Unfortunately, LVEF is load dependent and often overestimates LV function in MR. Global longitudinal strain, although also load dependent, appears more sensitive to LV dysfunction in patients with chronic MR and, as such, might give warning that LV function is declining before LVEF becomes abnormal.^{15,16,19,21} Thus, novel markers of LV systolic function, such as global longitudinal strain, may be useful adjuncts in assessing LV function in patients with chronic MR.

7.2.2.4. Diagnostic Testing: Cardiac Catheterization

Left ventriculography and hemodynamic measurements are useful when clinical assessment and noninvasive tests are inconclusive or discordant with regard to 1) severity of MR, 2) LV function, or 3) the need for surgery.¹ Noninvasive imaging is adequate for evaluation of MR in most cases. However, invasive hemodynamic evaluation may be necessary in some cases, especially when there is a clinical discrepancy between symptomatic status and noninvasive testing. Elevated filling pressures support a cardiac cause of dyspnea and may indicate severely abnormal pathophysiology even when the patient claims to be asymptomatic. Conversely, a normal invasive hemodynamic examination in a symptomatic

patient with what appears to be less than severe MR suggests a noncardiac cause for the symptoms. Hemodynamic evaluation can be especially helpful in patients with concomitant lung disease. Normal LA (or pulmonary artery wedge) pressure and a large transpulmonary gradient suggest pulmonary hypertension that is attributable to lung disease rather than mitral valve disease. Left ventriculography may also be of diagnostic benefit. Whereas echocardiographic-Doppler interrogation of the mitral valve measures flow velocity, ventriculography uses the density of contrast to determine the amount of blood flow from the LV to the LA. Although only semi-quantitative, a carefully performed ventriculogram can help in quantifying MR severity. Additional hemodynamic interventions, such as exercise or leg raising, may be helpful when the resting information is equivocal.

7.2.2.5. Diagnostic Testing: Exercise Testing

Recommendation for Diagnostic Testing: Exercise Testing for Chronic Primary MR Referenced studies that support the recommendation are summarized in Online Data Supplement 28.		
COR	LOE	Recommendation
2a	B-NR	1. In patients with primary MR (Stages B and C) and symptoms that might be attributable to MR, hemodynamic exercise testing using Doppler echocardiography or cardiac catheterization or cardiopulmonary exercise testing is reasonable. ¹⁻⁴

Synopsis

In a subset of apparently asymptomatic patients with severe primary MR, exercise testing with hemodynamics can provide additional diagnostic and prognostic information.

Recommendation-Specific Supportive Text

1. The onset of symptoms represents a key development in severe MR. However, some patients may not recognize their symptoms, may deny them, or may alter their lifestyle to remain asymptomatic. A formal treadmill exercise test can establish true exercise tolerance and can also form the baseline for future symptom assessment. Additional information about a cardiac or noncardiac limitation can be obtained from oxygen consumption measurements during exercise. When patients do complain of symptoms, they usually complain of dyspnea with exertion, yet noninvasive evaluation is usually made at rest. Exercise echocardiography or exercise invasive hemodynamics may add additional prognostic value beyond conventional exercise treadmill testing in patients with asymptomatic moderate or severe chronic primary MR.¹⁻⁴ MR may worsen during exercise, or filling pressures may become markedly abnormal, helping to demonstrate MR as the cause of the patient's dyspnea.¹⁻⁴

7.2.3. Medical Therapy

Recommendations for Medical Therapy for Chronic Primary MR Referenced studies that support the recommendations are summarized in Online Data Supplement 29.		
COR	LOE	Recommendations
2a	B-NR	1. In symptomatic or asymptomatic patients with severe primary MR and LV systolic dysfunction (Stages C2 and D) in whom surgery is not possible or must be delayed, GDMT for systolic dysfunction is reasonable. ¹⁻³
3: No Benefit	B-NR	2. In asymptomatic patients with primary MR and normal LV systolic function (Stages B and C1), vasodilator therapy is not indicated if the patient is normotensive. ⁴⁻⁸

Synopsis

In patients with primary MR, there is no convincing evidence that vasodilator therapy reduces MR severity. However, GDMT for LV systolic dysfunction or systemic hypertension should be implemented as in any patient with these conditions.

Recommendation-Specific Supportive Text

1. Patients with MR and LV dysfunction experience myocardial damage and HF. With onset of LV systolic dysfunction, surgery is usually indicated. However, in those patients in whom surgery (or transcatheter repair) is not performed or will be delayed, medical therapy for systolic dysfunction may be helpful to treat the LV dysfunction alone. Although data specific to patients with MR with LV dysfunction are sparse, treatment of such patients would consist of the standard regimen for HF, including beta-adrenergic blockade, ACE inhibitors or ARBs, and possibly aldosterone antagonists.¹⁻³ Perhaps the best data exist for the use of beta blockers,¹ which reverse LV dysfunction in experimental MR.² Patients who are receiving beta blockers may have better surgical outcomes and delayed onset of LV dysfunction as compared with those not taking these medications.³ ACE inhibition has not been effective in experimental MR with LV dysfunction. Because aldosterone antagonism is thought to work in part by inhibiting fibrosis, its role in MR, where little fibrosis occurs, is unclear.
2. Because vasodilator therapy appears to be effective in acute severe symptomatic MR, it seems reasonable to attempt afterload reduction in chronic asymptomatic MR with normal LV function in an effort to forestall the need for surgery. However, the results from the limited number of trials addressing this therapy have been disappointing, demonstrating little or no clinically important benefit.⁴⁻⁸ Conversely, because vasodilators decrease LV size and mitral closing force, they may increase

mitral valve prolapse, worsening rather than decreasing severity of MR.⁶ The foregoing does not apply to patients with concomitant hypertension. Hypertension must be treated because of the well-known morbidity and mortality associated with that condition and because increased LV systolic pressure by itself increases the systolic transmitral gradient and worsens severity of MR.

7.2.4. Intervention

Recommendations for Intervention for Chronic Primary MR Referenced studies that support the recommendations are summarized in Online Data Supplement 30.		
COR	LOE	Recommendations
1	B-NR	1. In symptomatic patients with severe primary MR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function. ^{1,2}
1	B-NR	2. In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF ≤60%, LVESD ≥40 mm) (Stage C2), mitral valve surgery is recommended. ^{3–10}
1	B-NR	3. In patients with severe primary MR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is degenerative disease, if a successful and durable repair is possible. ^{11–15}
2a	B-NR	4. In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF ≥60% and LVESD ≤40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1%, when it can be performed at a Primary or Comprehensive Valve Center. ^{4,13,16}
2b	C-LD	5. In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD <40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on ≥3 serial imaging studies, mitral valve surgery may be considered irrespective of the probability of a successful and durable repair. ¹⁶
2a	B-NR	6. In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, transcatheter edge-to-edge repair (TEER) is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year. ^{17,18}
2b	B-NR	7. In symptomatic patients with severe primary MR attributable to rheumatic valve disease, mitral valve repair may be considered at a Comprehensive Valve Center by an experienced team when surgical treatment is indicated, if a durable and successful repair is likely. ¹⁹
3: Harm	B-NR	8. In patients with severe primary MR where leaflet pathology is limited to less than one half the posterior leaflet, mitral valve replacement should not be performed unless mitral valve repair has been attempted at a Primary or Comprehensive Valve Center and was unsuccessful. ^{11–14,20–22}

Synopsis

Anterior and/or bileaflet primary mitral valve disease requires a complex and extensive repair,^{20,23–26} and durability of the repair is less certain than for simple posterior leaflet intervention. Freedom from reoperation is approximately 80%, and freedom from recurrent moderate or severe MR is 60% at 15 to 20 years in complex cases. These results are superior to the results of mitral valve replacement if the repair is performed at high-volume valve surgery centers,^{27–29} even in elderly patients.^{30,31} Repair should also be attempted, if possible, with other causes of severe MR, such as papillary muscle rupture, IE, and cleft mitral valve. However, the results of very complex repair in younger patients may be matched by the results of durable mechanical mitral valve replacement with careful management of anticoagulation. The Heart Valve Team should assign complex repairs to experienced mitral valve surgeons with established excellent operative and long-term outcomes. The probability of mitral valve repair rather than mitral valve replacement and overall outcome correlate with surgeon-specific mitral volumes.^{21,27} The hospital mortality rate is 50% lower, on average, in the highest-volume hospitals that perform 50 repairs per year. However, some low-volume hospitals outperform the median high-volume hospitals. This overlap suggests that hospital- or surgeon-specific volumes should not be used as a surrogate for actual surgeon-specific repair rates and outcomes (Figure 8). The management of patients with combined severe primary MR and AS is discussed in the Mixed Valve Disease section (Section 10.2.2).

Recommendation-Specific Supportive Text

1. Primary MR is a mechanical problem of the leaflet coaptation that has only a mechanical solution—that of mitral valve mechanical intervention. The onset of symptoms that results from severe MR worsens prognosis even when LV function appears to be normal,^{1,2} and the negative prognosis extends even to mild symptoms.² Thus, the onset of symptoms is an indication for prompt mitral valve surgery.
2. The goal of therapy in MR is to correct it before the onset of LV systolic dysfunction and its subsequent adverse effect on patient outcomes. The ideal time for mitral valve surgery is when the patient's LV approaches but has not yet reached the parameters that indicate systolic dysfunction (LVEF ≤60% or LVESD ≥40 mm).^{3–7,16} Because symptoms do not always coincide with LV dysfunction, imaging surveillance is used to plan surgery before severe dysfunction has occurred. If moderate LV dysfunction is already present, prognosis is worse after mitral valve operation.^{5–7,9,10,16} Thus, further delay (although symptoms are absent) will lead to greater LV dysfunction and a

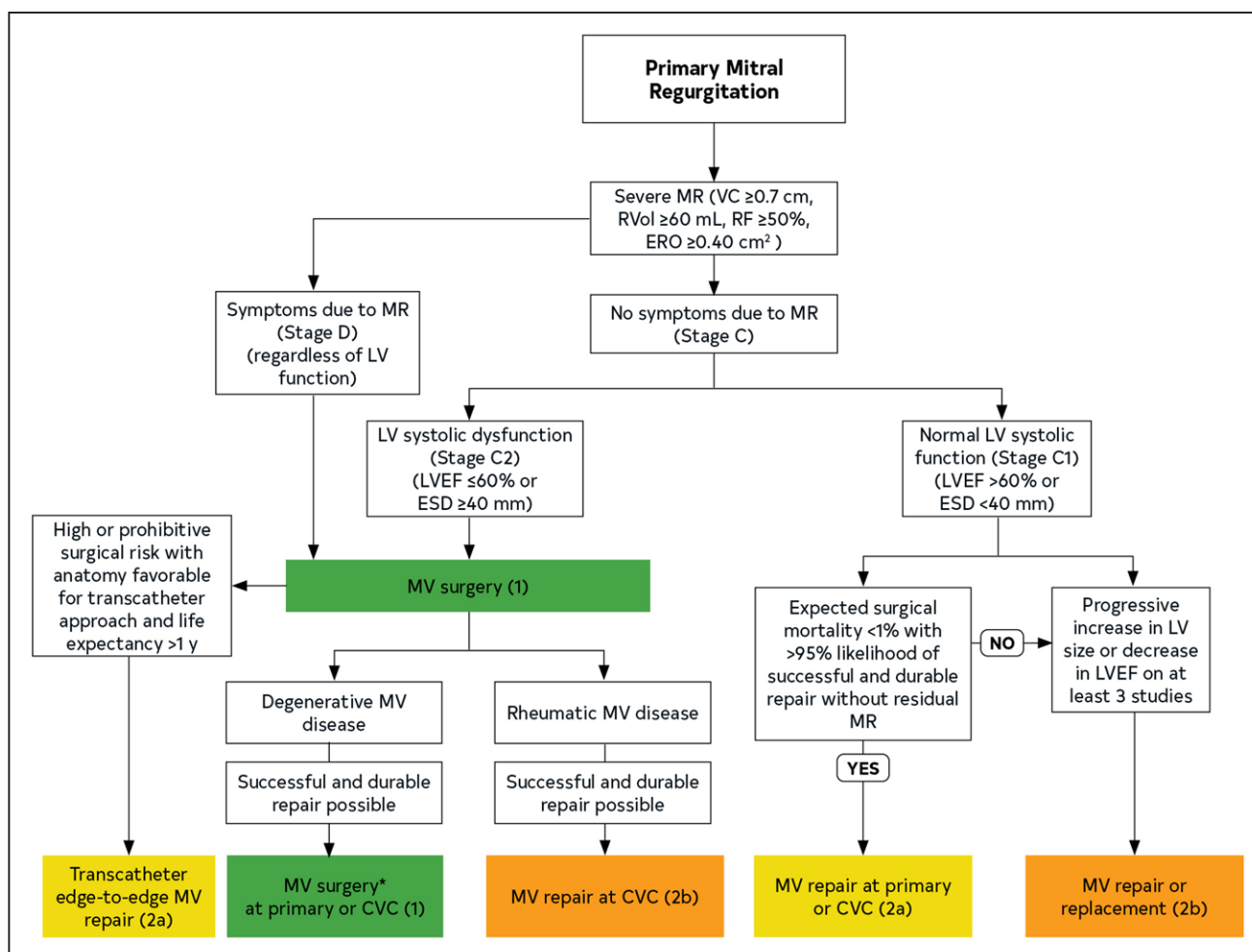


Figure 8. Primary MR.

Colors correspond to Table 2. *See Prosthetic Valve section (11.1.2) for choice of mitral valve replacement if mitral valve repair is not possible. CVC indicates Comprehensive Valve Center; ERO, effective regurgitant orifice; ESD, end-systolic dimension; LVEF, ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; RF, regurgitant fraction; RVol, regurgitant volume; and VC, vena contracta.

still worse prognosis. Because the loading conditions in MR allow continued late ejection into a lower-impedance LA, a higher cutoff for “normal” LVEF is used in MR than in other types of heart disease. Although it is clearly inadvisable to allow patients’ LV function to deteriorate beyond the benchmarks of an LVEF $\leq 60\%$ or LVESD ≥ 40 mm, some recovery of LV function can still occur even if these thresholds have been crossed.^{5,32}

3. Repair success increases with surgical volume and expertise, which is a principle guiding surgical referral.^{21,27} However, mitral valve replacement is preferable to a poor repair. The results of a minimally invasive approach may be similar to those of a full median sternotomy if the minimally invasive operation is performed by highly experienced surgeons.^{33–38} When leaflet dysfunction is limited so that only annuloplasty and repair of the posterior leaflet are necessary, an operative mortality rate of $<1\%$, long-term survival rate equivalent to that of the age-matched general population,

approximately 95% freedom from reoperation, and $>80\%$ freedom from recurrent moderate or severe MR at 15 to 20 years after operation are expected.^{23,24,39,40}

4. The onset of symptoms, LV dysfunction, or pulmonary hypertension worsens the prognosis for MR. Careful surveillance may result in timing of valve surgery before these negative sequelae occur. However, an attractive alternative strategy for treating severe chronic primary MR is to perform early mitral repair before these triggers are reached. Early mitral repair avoids the need for intensive surveillance and also obviates the possibility that patients might become lost to follow-up or delay seeing their clinician until advanced LV dysfunction has already ensued.^{4,13,16,22} For the early mitral repair strategy to be effective, a durable repair must be provided. An unwanted valve replacement and its attendant risks, or a failed repair necessitating reoperation, could be a complication of this

approach. Thus, there must be a high degree of certainty that a durable repair can be performed. This certainty comes from the track record of the surgical team in operating on the specific type of lesion under consideration. Thus, asymptomatic patients should be treated in a Comprehensive Valve Center.^{21,24,27–29} In excellent hands, patients with severe MR from flail leaflets who undergo early operation as opposed to watchful waiting have a lower risk of developing HF and lower mortality rates.^{4,13,15}

5. MR may lead to progressively more severe MR as the initial level of MR causes LV dilation, which increases stress on the mitral apparatus, causing further damage to the valve apparatus, more severe MR, and further LV dilation—thus initiating a perpetual cycle of ever-increasing LV volumes and MR. Longstanding volume overload leads to irreversible LV dysfunction and a poorer prognosis. Patients with severe MR who develop an LVEF <60% or LVESD ≥40 mm have already developed LV systolic dysfunction.^{5,6} One study has suggested that for LV function and size to return to normal after mitral valve repair, the LVEF should be >64% and LVESD <37 mm.¹⁶ Thus, when longitudinal follow-up demonstrates a progressive decrease of LVEF toward 60% or a progressive increase in LVESD approaching 40 mm, it is reasonable to consider intervention.⁴¹ In severe MR, TTE is recommended at 3- to 6-month intervals or more frequently as the ventricle enlarges.
6. Mitral transcatheter edge-to-edge repair (TEER) with the anterior and posterior leaflets clipped together at ≥1 locations is safe and effective in treating severely symptomatic patients with primary MR who are at high or prohibitive surgical risk.^{17,18,42} Studies of TEER with a mitral valve clip have demonstrated improved symptoms and a reduction in MR by 2 to 3 grades, leading to reverse remodeling of the LV. Superior outcomes were shown with surgery versus TEER, and thus it is only the patients who are at high or prohibitive risk for surgery for whom TEER is performed.
7. Rheumatic mitral valve disease is less suitable for mitral repair compared with complex degenerative disease. Durability of the repair is limited by thickened or calcified leaflets, extensive subvalvular disease with chordal fusion and shortening, and progression of rheumatic disease. Freedom from reoperation at 20 years, even in experienced hands, is in the 50% to 60% range. In a large series from Korea, repair was accomplished in 22% of patients operated on for rheumatic disease.¹⁹ One-third of these patients who underwent repair had significant stenosis or regurgitation at

10 years. Repair of rheumatic mitral valve disease should be limited to patients with less advanced disease in whom a durable repair can be accomplished or to patients in whom a mechanical prosthesis cannot be used because of anticoagulation management concerns.⁴³

8. Mitral valve repair is the procedure of choice for isolated severe primary MR limited to less than one-half of the posterior leaflet, and mitral valve replacement is inappropriate unless mitral valve repair has been attempted and was unsuccessful.^{11–14,21,22} Surgical repair of primary MR has been remarkably successful. Repair of isolated degenerative mitral disease, when leaflet dysfunction is sufficiently limited that only annuloplasty and repair of the posterior leaflet are necessary, has led to outcomes distinctly superior to those with biological or mechanical mitral valve replacement.^{11–14} Repair is associated with an operative mortality rate of <1%, long-term survival rate equivalent to that of age-matched general population, approximately 95% freedom from reoperation, and >80% freedom from recurrent moderate or severe (≥3) MR at 15 to 20 years after surgery.^{15,39} As much as one-half of the posterior leaflet may be excised, plicated, or resuspended. Posterior leaflet repair has become sufficiently standardized in this situation so that repair, rather than mitral valve replacement, is the standard of care. Execution of this procedure with a success rate ≥95% should be the expectation of every cardiac surgeon who performs mitral valve procedures.

7.3. Chronic Secondary MR

7.3.1. Stages of Chronic Secondary MR

In chronic secondary MR, the mitral valve leaflets and chords usually are normal or minimally thickened. Instead, MR is associated with severe LV dysfunction caused by CAD (ischemic chronic secondary MR) or idiopathic myocardial disease (nonischemic chronic secondary MR). The abnormal and dilated LV causes papillary muscle displacement, which in turn results in leaflet tethering with associated annular dilation that prevents adequate leaflet coaptation. Secondary MR may also develop because of LA dilation and enlargement of the mitral annulus, which often occurs with AF and other cardiomyopathies. There are instances in which both primary and secondary MR are present. The best therapy for chronic secondary MR is not clear because MR is only one component of the disease, and restoration of mitral valve competence is not curative. The optimal criteria for defining severe secondary MR have been controversial. Compared with primary MR, adverse outcomes in secondary MR are associated with a smaller

calculated ERO; the severity of secondary MR may increase over time because of adverse remodeling of the LV or mitral annulus; and Doppler methods for calculations of ERO area by the flow convergence method may underestimate severity because of the crescentic shape of the regurgitant orifice.^{1,2} Even so, on the basis of the criteria used for determination of “severe” MR in RCTs of surgical intervention for secondary MR,^{3–6} the recommended definition of severe secondary MR is now the same as for primary MR (ERO ≥ 0.4 cm² and regurgitant volume ≥ 60 mL) (Table 18).

7.3.2. Diagnosis of Chronic Secondary MR

Recommendations for Diagnosis of Secondary MR Referenced studies that support the recommendations are summarized in Online Data Supplement 31.		
COR	LOE	Recommendations
1	B-NR	1. In patients with chronic secondary MR (Stages B to D), TTE is useful to establish the etiology and to assess the extent of regional and global LV remodeling and systolic dysfunction, severity of MR, and magnitude of pulmonary hypertension. ^{1,2}
1	C-EO	2. In patients with chronic secondary MR (Stages B to D), noninvasive imaging (stress nuclear/PET, CMR, or stress echocardiography), coronary CT angiography, or coronary arteriography is useful to establish etiology of MR and to assess myocardial viability.
1	B-NR	3. In patients with chronic secondary MR with severe symptoms (Stage D) that are unresponsive to GDMT who are being considered for transcatheter mitral valve interventions, TEE is indicated to determine suitability for the procedure. ^{3–8}
1	C-EO	4. In patients with chronic secondary MR undergoing transcatheter mitral valve intervention, intraprocedural guidance with TEE is recommended. ^{4,7,9–13}

Synopsis

In symptomatic patients with chronic secondary MR, TTE is the initial diagnostic modality. Assessment of the coronary anatomy and myocardial viability may be helpful in management if ischemic MR is suspected. If transcatheter mitral valve intervention is contemplated, TEE determines suitability for the procedure and guides the procedure.¹

Recommendation-Specific Supportive Text

1. TTE is essential in patients with MR to identify patients with primary MR and those with secondary forms of MR. In general, in patients with LV systolic dysfunction and symptoms of HF, the presence of chronic secondary MR of any severity is associated with a worse prognosis than that seen in the absence of MR. Most patients with

secondary MR have global LV dysfunction, but in some patients, a limited but strategically placed wall motion abnormality may also cause chronic secondary MR. An initial TTE helps establish the cause of chronic secondary MR and also serves as a baseline for future comparisons. In patients with secondary MR, severe MR is defined as an ERO ≥ 40 mm², but outcome studies have shown poor prognosis in those with moderate MR (ERO ≥ 20 mm²).^{1,2}

2. Prognosis is poor for both ischemic and non-ischemic MR, but ischemic MR lends itself to the possibility of revascularization and potential improvement in LV function if CAD has led to large areas of hibernating viable myocardium. Long-term results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial demonstrated an improved 10-year survival rate in patients with ischemic cardiomyopathy and LVEF $<35\%$ who underwent CABG plus GDMT as compared with those randomized to GDMT alone. CT angiography is usually adequate to rule out significant CAD and thus rule out ischemic MR. If CAD is detected and noninvasive testing demonstrates areas of viability, coronary arteriography is pursued to better define the anatomy for potential revascularization.^{14,15} Although the presence of myocardial viability did not determine the effect of revascularization on survival in the STICH trial, there is a subset of patients with viable myocardium in whom the ischemic MR will respond to revascularization.^{16–18}
3. Clinical trials have identified anatomic considerations, detectable by TEE, that can identify patients with secondary MR who have a valve morphology amenable to TEER. In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial of patients with secondary MR and HF, exclusion criteria included vertical coaptation length <2 mm in valves with leaflet tethering, evidence of calcification in the grasping area of the A2 or P2 scallops, presence of a significant cleft of A2 or P2 scallops, and lack of both primary and secondary chordal support. These are similar criteria to the earlier EVEREST trial. TEE is standard preprocedural imaging to determine suitability for TEER.^{3–8}
4. During mitral TEER, TEE assists in guiding positioning of the clip(s), assessing success of the procedure, determining whether more than a single clip is necessary to reduce MR, and assuring that the clip(s) has not created MS.^{4,7,9–13}

Table 18. Stages of Secondary MR

Stage	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	Normal valve leaflets, chords, and annulus in a patient with CAD or cardiomyopathy	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.30 cm	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction	Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of central coaptation of the mitral leaflets	ERO <0.40 cm ² † Regurgitant volume <60 mL Regurgitant fraction <50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction attributable to primary myocardial disease	Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.40 cm ² † Regurgitant volume ≥60 mL‡ Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction attributable to primary myocardial disease	Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.40 cm ² † Regurgitant volume ≥60 mL‡ Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction attributable to primary myocardial disease	HF symptoms attributable to MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient.

Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO because of the crescentic shape of the proximal convergence.

‡May be lower in low-flow states.

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

7.3.3. Medical Therapy

Recommendations for Medical Therapy for Secondary MR Referenced studies that support the recommendations are summarized in Online Data Supplement 31.		
COR	LOE	Recommendations
1	A	1. Patients with chronic severe secondary MR (Stages C and D) and HF with reduced LVEF should receive standard GDMT for HF, including ACE inhibitors, ARBs, beta blockers, aldosterone antagonists, and/or sacubitril/valsartan, and biventricular pacing as indicated. ¹⁻¹¹
1	C-EO	2. In patients with chronic severe secondary MR and HF with reduced LVEF, a cardiologist expert in the management of patients with HF and LV systolic dysfunction should be the primary MDT member responsible for implementing and monitoring optimal GDMT. ^{9,12}

Synopsis

GDMT for HF with reduced LVEF in patients with severe secondary MR should be provided, in conjunction with a cardiology expert, in the management of HF.

Recommendation-Specific Supportive Text

1. Chronic secondary MR usually develops as a result of LV systolic dysfunction. Thus, standard GDMT for HF forms the mainstay of therapy. Diuretics, beta blockers, ACE inhibitors or ARBs, and aldosterone antagonists help improve symptoms and/or prolong life in patients with HF in general and probably do so even when HF is complicated by chronic secondary MR. GDMT can reduce LV volumes (reverse remodeling) in many patients, which reduces severity of secondary MR.¹⁻¹¹
2. Secondary MR is often responsive to GDMT (including coronary revascularization or cardiac resynchronization therapy in appropriate patients). Optimization of GDMT should be under the supervision of a cardiologist expert in the treatment of patients with HF to achieve optimal results and to determine with the MDT when symptoms are truly refractory to GDMT before decisions are made for surgical or transcatheter treatment.^{9,12}

7.3.4. Intervention

Recommendations for Intervention for Secondary MR		
Referenced studies that support the recommendations are summarized in Online Data Supplement 31.		
COR	LOE	Recommendations
2a	B-R	1. In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg. ¹⁻⁸
2a	B-NR	2. In patients with severe secondary MR (Stages C and D), mitral valve surgery is reasonable when CABG is undertaken for the treatment of myocardial ischemia. ⁹⁻¹⁵
2b	B-NR	3. In patients with chronic severe secondary MR from atrial annular dilation with preserved LV systolic function (LVEF ≥50%) who have severe persistent symptoms (NYHA class III or IV) despite therapy for HF and therapy for associated AF or other comorbidities (Stage D), mitral valve surgery may be considered. ¹⁶⁻²⁰
2b	B-NR	4. In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent severe symptoms (NYHA class III or IV) while on optimal GDMT for HF (Stage D), mitral valve surgery may be considered. ^{9,12,21-43}
2b	B-R	5. In patients with CAD and chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) (Stage D) who are undergoing mitral valve surgery because of severe symptoms (NYHA class III or IV) that persist despite GDMT for HF, chordal-sparing mitral valve replacement may be reasonable to choose over downsized annuloplasty repair. ^{9,12,21-32,44-47}

Synopsis

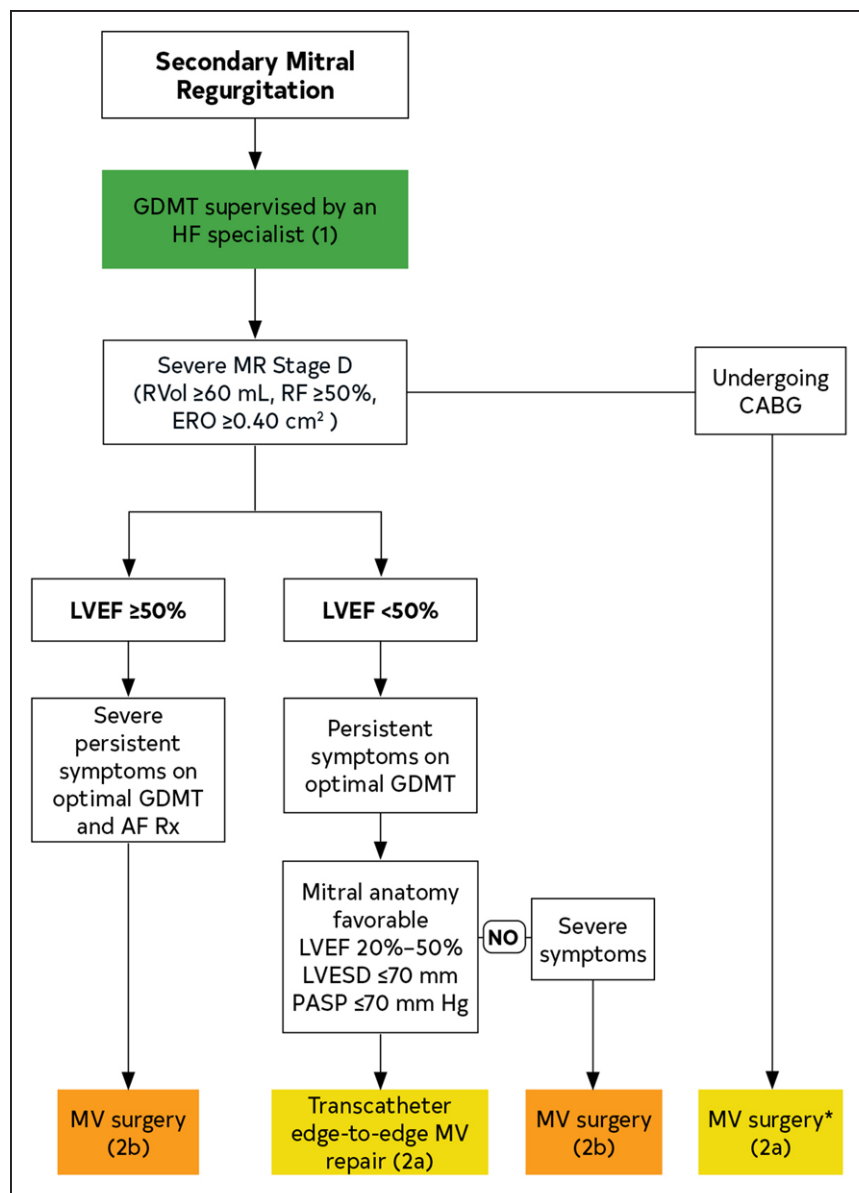
Mitral TEER is indicated to improve symptoms and prolong life in a select subset of patients with chronic severe secondary MR, LV systolic dysfunction, and persistent severe symptoms while on optimal GDMT. Surgery may improve symptoms in these patients, with mitral valve replacement preferred over repair. A subset of patients with severe MR attributable to AF may benefit from mitral valve surgery and concomitant atrial maze procedure (Figure 9).

Recommendation-Specific Supportive Text

1. The COAPT trial of transcatheter treatment of secondary MR demonstrated improvement in survival, hospitalization, symptoms, and quality of life in patients with persistent symptoms despite optimization of GDMT who were randomized to TEER, as compared with those randomized to continued GDMT. In contrast, MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve

Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) enrolled patients with greater degrees of LV enlargement and less severe MR (mean ERO area 0.31 cm² versus 0.41 cm²) and reported no benefit of TEER in reducing the composite endpoint of death or hospitalization as compared with medical therapy. In addition, the inclusion criterion in MITRA-FR of an LVESD up to 70 mm represents extreme dilation; in contrast, in the COAPT trial, the mean LVESD was smaller (52±9 mm), and even the LVEDD rarely exceeded 70 mm (mean 62±7 mm). Thus, the enrollment criteria in COAPT trial (LVEF between 20% and 50%, LVESD ≤70 mm, pulmonary artery systolic pressure ≤70 mmHg, and persistent symptoms [NYHA class II, III, or IV] while on optimal GDMT) are the current standard selection criteria for TEER for secondary MR. Observational studies have suggested that a greater reduction in MR severity with TEER is associated with greater LV and LA reverse remodeling.^{1-8,48,49} The exact anatomy and mechanism of MR also needs to be taken into consideration when determining candidacy for transcatheter repair.

2. There is no proof that surgical correction of chronic secondary MR is effective in prolonging life, but observational studies and a substudy of the randomized STICH trial suggest that it is wise to address the mitral valve during CABG for severe CAD when secondary MR is severe. Although it may be hoped that the revascularization will recruit hibernating myocardium and reduce chronic secondary MR, this has not been demonstrated, and failing to correct chronic severe secondary MR may leave the patient with severe residual MR. The risks and benefits of additional surgical interventions should be weighed in patients with LV systolic dysfunction.⁹⁻¹³ For patients with secondary MR undergoing operation for other valve disease, see Section 10.2 (Timing of Intervention for Mixed Valve Disease).
3. MR may develop in patients with preserved LV systolic function who have progressive LA dilation, leading to enlargement of the mitral annulus and malcoaptation of the leaflets.^{51,52} This may arise in conditions such as HF with preserved LVEF, restrictive cardiomyopathy, and nonobstructive hypertrophic cardiomyopathy. These patients often have associated AF, which may contribute to the progression of LA and annular dilation, thus increasing the severity of MR.^{18,53} and successful ablation of AF may reduce or eliminate MR.⁵³ Isolated annular dilation accounts for <20% of patients referred for surgery of severe MR in the STS database, but it is also the etiology with

**Figure 9. Secondary MR.**

Colors correspond to Table 2. *Chordal-sparing MV replacement may be reasonable to choose over downsized annuloplasty repair. AF indicates atrial fibrillation; CABG, coronary artery bypass graft; ERO, effective regurgitant orifice; GDMT, guideline-directed management and therapy; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, medication.

the highest mitral valve repair rates (85%).^{16,17} The limited data addressing mitral valve repair in patients with annular dilation related to AF indicate low operative risk.^{18–20}

- There is limited evidence that mitral valve surgery improves survival in symptomatic patients with secondary MR. In addition, surgery may improve symptoms and quality of life in these patients whose symptoms persist despite GDMT. Small RCTs demonstrate that mitral valve surgery reduces chamber size and improves peak oxygen consumption in chronic severe secondary MR. Ischemic or dilated cardiomyopathy presents different challenges for mitral repair. Regurgitation is caused by annular dilation, as well as by apical and lateral displacement of the papillary muscles. New techniques have facilitated mitral repair in this situation, but durability of the repair is

dependent primarily on regression or progression of ventricular dilation. If the heart continues to dilate, long-term durability of the repair is moot; the survival of the patient is limited.^{9,12,21–43}

- In an RCT of mitral valve repair versus mitral valve replacement in patients with severe ischemic MR, there was no difference between repair and mitral valve replacement in survival rate or LV remodeling at 2 years. However, the rate of recurrence of moderate or severe MR over 2 years was higher in the repair group than in the replacement group, leading to a higher incidence of HF and repeat hospitalization. The lack of apparent benefit of valve repair over valve replacement in secondary MR versus primary MR, with less durable repairs in secondary MR, highlights that primary and secondary MR are 2 different diseases.^{9,12,21–32,44–47}

8. TRICUSPID VALVE DISEASE

8.1. Classification and Stages of TR

Trace to mild degrees of TR of no physiological consequence are commonly detected on TTE in subjects with anatomically normal valves. However, significant or worsening TR is associated with poor long-term outcomes.^{1–7} Primary disorders of the tricuspid apparatus that can lead to more significant degrees of TR include rheumatic disease, IE, congenital disease (Ebstein's), myxomatous changes, and other problems affecting the tricuspid valve leaflets (blunt chest trauma, carcinoid, drugs, and radiation) (Table 19). A growing number of patients develop significant TR from iatrogenic etiologies (device leads and endomyocardial biopsies).^{8–10} Most cases of significant TR are secondary and related to tricuspid annular dilation and leaflet tethering in the setting of RV remodeling because of pressure or volume overload, as seen in patients with pulmonary hypertension (primary or secondary to left-sided heart disease) or dilated cardiomyopathies.^{11–13} In addition, there appears to be a subgroup of patients with significant isolated TR attributable primarily to annular dilation, usually associated with AF in the absence of pulmonary hypertension or LV systolic dysfunction.^{2,14–18} Table 20 shows the stages of TR as defined for other valve lesions. Asymptomatic patients with severe TR (Stage C) present with an elevated central venous pressure and imaging evidence of significant TR.

Symptomatic patients with severe TR (Stage D) have symptoms of fatigue, abdominal bloating, and peripheral edema. End-organ damage, such as hepatic failure and renal failure, is an adverse consequence of Stage D TR that markedly affects survival.^{19–23} The severity of TR can be dynamic and dependent on changes in preload and pulmonary pressure.

8.2. Tricuspid Regurgitation

8.2.1. Diagnosis of TR

Recommendations for Diagnosis of TR		
COR	LOE	Recommendations
1	C-LD	1. In patients with TR, TTE is indicated to evaluate the presence and severity of TR, determine the etiology, measure the sizes of the right-sided chambers and inferior vena cava, assess RV systolic function, estimate pulmonary artery systolic pressure, and characterize any associated left-sided heart disease. ^{1,2}
2a	C-LD	2. In patients with TR, invasive measurement of the cardiac index, right-sided diastolic pressures, pulmonary artery pressures, and pulmonary vascular resistance, as well as right ventriculography, can be useful when clinical and noninvasive data are discordant or inadequate. ^{3–5}

Table 19. Classification of TR

Primary	Secondary
Rheumatic	Pulmonary hypertension with RV remodeling (primary or secondary to left-sided heart disease)
Infective endocarditis	Dilated cardiomyopathy
Iatrogenic (device leads, endomyocardial biopsy)	Annular dilation (associated with AF)*
Congenital (eg, Ebstein's, levo-transposition of the great arteries)	RV volume overload (shunts/high output)
Other (eg, trauma, carcinoid, drugs, irradiation)	

*Isolated TR is associated with AF and has LVEF >60%, pulmonary artery systolic pressure <50 mm Hg, and no left-sided valve disease, with normal-appearing tricuspid valve leaflets.

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; RV, right ventricular; and TR, tricuspid regurgitation.

Synopsis

TTE can determine the etiology of TR and its effect on the RV. Cardiac catheterization is of clinical value if the information from TTE is inadequate or discordant with the clinical presentation.^{6–10}

Recommendation-Specific Supportive Text

1. TTE can distinguish primary TR (abnormal valve leaflets) from secondary TR (normal valve leaflets), define any associated left-sided valvular or myocardial disease, and provide an estimate of pulmonary artery systolic pressure.^{11–15} Characterization of the severity of TR relies on an integrative assessment of multiple parameters, as recommended by the American Society of Echocardiography and European Association of Echocardiography,^{1,2} but many limitations remain. In patients with TR undergoing left-sided valve surgery, an annular diastolic diameter >40 mm (or >21 mm/m²) indicates an increased risk of persistent or progressive TR after isolated mitral valve surgery.¹³ Pulmonary artery systolic pressure is estimated from maximal TR velocity. Assessment of RV systolic function is challenged by geometric and image acquisition constraints, as well as by variability in RV loading condition.^{16,17} Normal RV systolic function is defined by several parameters, including tricuspid annular plane systolic excursion >16 mm, tricuspid valve systolic annular velocity >10.0 cm/s, and RV end-systolic area <20.0 cm² or fractional area change >35%. Other imaging modalities, such as 3D TEE, magnetic resonance imaging, and CT scan, may provide more accurate information on the status of the RV.
2. When physical examination and TTE data on estimated pulmonary artery systolic pressure are either discordant or inadequate, invasive measurement of pulmonary artery pressures and pulmonary vascular resistance can be helpful to guide

Table 20. Stages of TR

Stage	Definition	Valve Hemodynamics	Hemodynamic Consequences	Clinical Symptoms and Presentation
B	Progressive TR	Central jet <50% RA Vena contracta width <0.7 cm ERO <0.40 cm ² Regurgitant volume <45 mL	None	None
C	Asymptomatic severe TR	Central jet ≥50% RA Vena contracta width ≥0.7 cm ERO ≥0.40 cm ² Regurgitant volume ≥45 mL Dense continuous wave signal with triangular shape Hepatic vein systolic flow reversal	Dilated RV and RA Elevated RA with “c-V” wave	Elevated venous pressure No symptoms
D	Symptomatic severe TR	Central jet ≥50% RA Vena contracta width ≥0.7 cm ERO ≥0.40 cm ² Regurgitant volume ≥45 mL Dense continuous wave signal with triangular shape Hepatic vein systolic flow reversal	Dilated RV and RA Elevated RA with “c-V” wave	Elevated venous pressure Dyspnea on exertion, fatigue, ascites, edema

c-V wave indicates systolic positive wave; ERO, effective regurgitant orifice; RA, right atrial; RV, right ventricular; and TR, tricuspid regurgitation.

clinical decision-making in individual patients.^{3–5} A weak TR signal or the presence of severe TR may result in underestimation of pulmonary systolic pressure; direct invasive measurement can resolve this uncertainty. Data from invasive measurement are essential for patients in whom the cause of pulmonary hypertension is uncertain or when assessment of pulmonary vascular reactivity after vasodilator challenge is needed. Direct measurements of right atrial pressure may also be useful for clinical decision-making. Right ventriculography may further aid in the evaluation of the severity of TR and the status of the RV. Thermodilution cardiac output measurements may be inaccurate with severe TR, and thus a Fick cardiac output should be measured to apply to the calculation of pulmonary resistance.

8.2.2. Medical Therapy

Recommendations for Medical Therapy for TR		
COR	LOE	Recommendations
2a	C-EO	1. In patients with signs and symptoms of right-sided HF attributable to severe TR (Stages C and D), diuretics can be useful.
2a	C-EO	2. In patients with signs and symptoms of right-sided HF attributable to severe secondary TR (Stages C and D), therapies to treat the primary cause of HF (eg, pulmonary vasodilators to reduce elevated pulmonary artery pressures, GDMT for HF with reduced LVEF, or rhythm control of AF) can be useful ^{1,2}

Synopsis

Diuretic therapy treats the systemic congestion in patients with severe symptomatic TR. In patients with secondary TR, treatment of the underlying primary cause may decrease the severity of the TR.

Recommendation-Specific Supportive Text

1. Patients with severe TR usually present with signs or symptoms of right-sided HF, including peripheral edema and ascites. Low-salt diet and support stockings may be helpful. Diuretics can be used to decrease volume overload in these patients. Loop diuretics are typically provided and may relieve systemic congestion, but their use can be limited by worsening low-flow syndrome. Aldosterone antagonists may be of additive benefit, especially in the setting of hepatic congestion, which may promote secondary hyperaldosteronism.
2. Medical therapies for management of severe TR (Stages C and D) are limited. Attention should be focused on the underlying etiologies in patients with secondary TR. Reduction of pulmonary artery pressures and pulmonary vascular resistance with specific pulmonary vasomodulators may be helpful to reduce RV afterload and secondary TR in selected patients with pulmonary hypertension.^{1,2} GDMT is effective for secondary TR attributable to HF with reduced LVEF. Restoration of normal sinus rhythm may be effective for secondary TR attributable to annular dilation associated with AF.^{3,4}

8.2.3. Timing of Intervention

Recommendations for Timing of Intervention Referenced studies that support the recommendations are summarized in Online Data Supplement 32.		
COR	LOE	Recommendations
1	B-NR	1. In patients with severe TR (Stages C and D) undergoing left-sided valve surgery, tricuspid valve surgery is recommended. ¹⁻⁸
2a	B-NR	2. In patients with progressive TR (Stage B) undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either 1) tricuspid annular dilation (tricuspid annulus end diastolic diameter >4.0 cm) or 2) prior signs and symptoms of right-sided HF. ³⁻¹⁰
2a	B-NR	3. In patients with signs and symptoms of right-sided HF and severe primary TR (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ¹¹⁻¹⁴
2a	B-NR	4. In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations. ^{11,12,15-19}
2b	C-LD	5. In asymptomatic patients with severe primary TR (Stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered. ^{12,20}
2b	B-NR	6. In patients with signs and symptoms of right-sided HF and severe TR (Stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction. ^{1,2,11,18}

Synopsis

Treatment of secondary TR is targeted at pulmonary hypertension or myocardial disease. Surgical treatment is performed for selected patients with TR at the time of surgery for left-sided valve lesions to treat severe TR (Stages C and D) and to prevent later development of severe TR in patients with progressive TR (Stage B). Surgical intervention should be considered for selected patients with isolated TR (either primary TR or secondary TR attributable to annular dilation in the absence of pulmonary hypertension or dilated cardiomyopathy). Intervention for severe isolated TR had a high reported operative mortality rate (up to 8% to 20%), but most of these interventions were performed after end-organ damage.²¹ However, outcomes of patients with severe primary TR are poor with medical management. There is renewed interest in earlier surgery for patients with severe isolated TR before the onset of severe RV dysfunction or end-organ damage.^{2,11,12,18,19,22} This interest is attributable to 1) an increasing number of patients presenting with right-sided HF from isolated TR,²³⁻²⁵ 2) more advanced surgical techniques, and 3) better selection

processes, resulting in a lower operative risk with documented improvement in symptoms (Figure 10).^{11,12,15-19}

There is growing interest in the development of catheter-based therapies for these patients with severe isolated TR.^{26,27}

Recommendation-Specific Supportive Text

1. Severe TR of either a primary or secondary etiology may not improve predictably after treatment of the left-sided valve lesion and reduction of RV afterload; as such, severe TR should be addressed as part of the index procedure.^{1,2,28-31} Reoperation for severe, isolated TR after left-sided valve surgery is associated with a perioperative mortality rate of 10% to 25%.^{1,29} Tricuspid valve repair does not add appreciably to the risks of surgery.^{1,2,28-31} There has been a significant increase in the number of tricuspid valve repairs performed for this indication over the past decade. Tricuspid valve repair is preferable to replacement, but replacement may be necessary if there is marked dilation of the annulus or intrinsic disease of the tricuspid leaflets.^{28,31} Observational data have shown a lower operative risk with tricuspid valve repair than with replacement, but this may be related to patient selection, given that the latter would be inserted in patients with a severely dilated annulus and abnormal leaflets to prevent recurrent or residual regurgitation. The risks and benefits of tricuspid valve operation should be carefully considered in the presence of severe RV systolic dysfunction or irreversible pulmonary hypertension because of the possibility of RV failure after operation.
2. Left uncorrected at the time of left-sided valve surgery, mild or moderate degrees of secondary TR may progress over time in approximately 25% of patients and result in reduced long-term functional outcome and survival.³² Risk factors for persistence or progression of TR include tricuspid annulus dilation (>40 mm diameter or 21 mm/m² diameter indexed to body surface area on pre-operative TTE measured at end diastole; >70 mm diameter on direct intraoperative measurement of the intercommissural distance), degree of RV dysfunction or remodeling, leaflet tethering height, pulmonary artery hypertension, AF, and intra-annular RV pacemaker or implantable cardioverter-defibrillator leads.^{3-10,33-36} Several observational studies and one prospective RCT have demonstrated the benefit of tricuspid repair at the time of mitral valve surgery for progressive TR (Stage B) with tricuspid annulus dilation on echocardiographic and functional parameters, although data on outcomes such as survival and major adverse events are lacking.^{3-10,33-35} Because

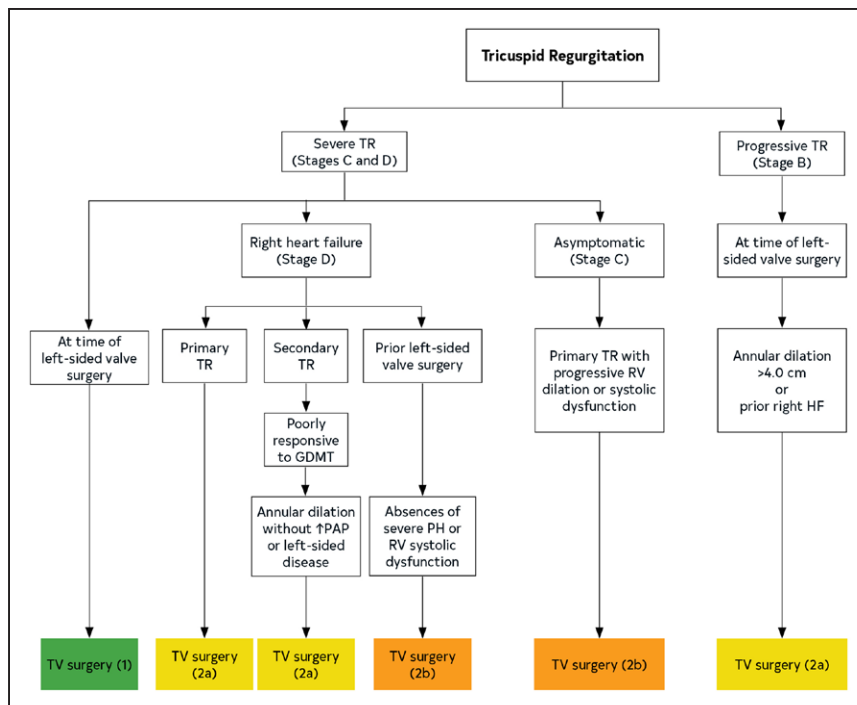


Figure 10. Tricuspid regurgitation.

Colors correspond to Table 2. GDMT indicates guideline-directed management and therapy; HF, heart failure; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RV, right ventricular; TR, tricuspid regurgitation; and TV, tricuspid valve.

the severity of TR may be dynamic, dependent on the preload and pulmonary pressures, a past history of signs or symptoms of right-sided HF indicates the propensity to develop more severe TR and should be considered an indication for concomitant tricuspid valve repair.

- In patients with symptomatic severe primary TR, reduction or elimination of the regurgitant volume load by tricuspid valve surgery can alleviate systemic venous and hepatic congestion and decrease reliance on diuretics.^{11,12,20} Patients with severe congestive hepatopathy may also benefit from surgery to prevent irreversible cirrhosis of the liver. Quality and duration of long-term survival are related to residual RV function. In patients with severe symptomatic primary TR from either device leads or endomyocardial biopsy, TR develops rapidly, and surgery can be done before the onset of RV dysfunction.^{11,37} Correction of symptomatic severe primary TR (Stage D) in patients without left-sided valve disease would preferentially be performed before the onset of significant RV dysfunction or end-organ damage. Randomized studies of early intervention are lacking, and the benefit might be limited by the risk of intervention, suboptimal reduction in TR severity, or suboptimal durability of currently available approaches to tricuspid valve repair and replacement.
- There is now recognition that TR can develop in association with AF and annular dilation (a form of secondary TR).^{23–25} Notably, AF-related TR appears to represent a fundamentally different pathophysiology from other forms of secondary TR, with greater

basal dilation and annular enlargement, as compared with the RV elongation with leaflet tethering seen in patients who have secondary TR caused by pulmonary hypertension or myocardial disease.²⁴ These patients with AF-related TR have rapid progression of TR severity and right-sided chamber dilation. In appropriately selected symptomatic patients with AF-related severe TR, quality of life and symptoms can be improved by surgical intervention for TR. In patients undergoing intervention, overall outcomes are better in those without severe RV dysfunction or end-organ damage. Newer surgical techniques and a better selection process resulted in an acceptable operative mortality rate (<4% to 5%) for isolated TR in selected patients.^{2,11,12,15–19,22,38}

- The optimal timing of tricuspid valve surgery for asymptomatic or minimally symptomatic patients with severe primary TR has not been established. Extrapolation from limited experiences reported for patients with stable carcinoid heart disease and patients with a flail tricuspid leaflet, as well as application of the management principles adopted for patients with severe MR, suggest that serial assessments of RV size and function might trigger consideration of corrective surgery in selected patients with severe primary TR when a pattern of continued deterioration can be established and the surgical risk is considered acceptable.^{13,14} In otherwise healthy patients without other comorbidities, such as patients with severe TR attributable to trauma, the surgical risk associated with tricuspid valve operation is low (<1% to 2% operative mortality

rate) in the absence of RV dysfunction or pulmonary hypertension.

6. Isolated tricuspid valve surgery for severe TR historically has been performed relatively late in the natural history of the disease, when patients have become symptomatic with signs of right-sided HF. Unadjusted mortality rates for isolated tricuspid valve surgery have therefore exceeded those reported for isolated aortic or mitral valve surgery, and this trend has been even more pronounced for reoperative tricuspid surgery late after left-sided valve surgery.^{1,2,39} This high reoperative mortality rate is likely related to the advanced nature of RV failure encountered at the time of the second procedure, residual pulmonary hypertension, LV dysfunction, and other valve abnormalities. The hazards imposed by reoperation have influenced decision-making for initial repair of functional TR at the time of left-sided valve surgery in an attempt to prevent the development of severe TR later after the left-sided valve surgery. However, if there is no significant pulmonary hypertension or severe RV systolic dysfunction, operation for severe symptomatic isolated TR years after surgery for left-sided disease may improve symptoms of right-sided HF, if done before the onset of severe RV dysfunction or end-organ damage with either hepatic or renal dysfunction.^{11,18}

9. PULMONIC VALVE DISEASE

See guidelines for the management of adults with congenital heart disease.¹

10. MIXED VALVE DISEASE

10.1. Diagnosis of Mixed VHD

Recommendations for Diagnosis and Follow-Up of Patients With Mixed Valve Disease		
COR	LOE	Recommendations
1	C-EO	1. For patients with mixed valve disease, TTE is recommended to assess the etiology, severity, and pathophysiological impact.
2a	C-EO	2. In patients with ambiguous symptoms that are suspected to be attributable to mixed mitral valve disease, further assessment of filling pressure by using biomarkers or invasive hemodynamic measurements at rest or with exercise is reasonable.

Synopsis

Mixed valve disease is either 1) stenosis and regurgitation of a single valve or 2) stenosis or regurgitation of 2 separate valves. Mixed valve disease presents a special diagnostic challenge to the clinician in assessing the impact of the lesions on cardiac remodeling, ventricular

function, and timing of intervention.^{1–5} For many patients with mixed valve disease, there is a predominant valve lesion (ie, stenosis versus regurgitation; mitral versus aortic), and symptoms and pathophysiology resemble those of a pure dominant lesion. When pressure overload predominates, there is usually concentric hypertrophy, whereas volume overloads cause chamber dilation and eccentric hypertrophy; management should follow the guidelines for the predominant lesion. However, in other cases, patients present with a more balanced picture, with the mixed pathophysiology making patient management difficult. It may be that neither lesion by itself reaches Stage C as described in previous sections for pure lesions, yet the lesions may be, in combination, severe enough to impact outcome. Mixed valve disease was primarily attributable to rheumatic disease in the past, but it is now more frequently seen with degenerative disease or after prior chest radiation.⁵ Decision-making for patients with mixed valve disease is frequently complex and may require referral to or consultation with a Comprehensive Valve Center.

Recommendation-Specific Supportive Text

1. The complex nature of mixed valve disease requires a comprehensive imaging approach that involves assessing each lesion separately and then collectively judging how the lesions affect the patient's overall presentation. TTE is the standard modality for measuring jet velocities, valve areas, regurgitant flow, and regurgitant orifice areas. TTE establishes the baseline for pathoanatomy and pathophysiology from which comparison is made as the lesions progress over time. Doppler hemodynamics have been validated for patients with single-valve disease but have not necessarily been studied in patients with multivalve disease. Limitations exist for assessment of calculations, such as those for valve areas, because of differential flows with multivalve disease.^{2–5}
2. The complex nature of mixed valve disease makes it necessary to consider all available data to reach a final management decision. Although natural history data for many types of mixed valve disease are lacking, it is reasonable to assume that the onset of symptoms is a negative prognostic occurrence, as it is for all other valve lesions. The difficulty may lie in attributing such symptoms to the mixed valve disease at hand, especially if TTE demonstrates moderate but not severe mixed disease. Elevated BNP and elevated filling pressures at catheterization, either at rest or with exercise, support that cardiac disease is the cause of the patient's symptoms and may help to further quantify lesion severity.

10.2. Timing of Intervention for Mixed VHD

10.2.1. Intervention for Mixed AS and AR

Recommendations for Timing of Intervention for Mixed AS and AR Referenced studies that support the recommendations are summarized in Online Data Supplement 13.		
COR	LOE	Recommendations
1	B-NR	1. In symptomatic patients with combined AS and AR and a peak transvalvular jet velocity of at least 4.0 m/s or a mean transvalvular gradient of at least 40 mm Hg, AVR is recommended. ^{1,2}
1	C-EO	2. In asymptomatic patients with combined AS and AR who have a jet velocity of ≥ 4.0 m/s with an LVEF $< 50\%$, SAVR is recommended. ^{1,2}

Synopsis

The indications for AVR in patients with combined AS and AR and a peak transvalvular jet velocity of ≥ 4.0 m/s are the same as for patients with severe isolated AS.

Recommendation-Specific Supportive Text

- Currently, isolated moderate AS or moderate AR is placed in Stage B, progressive disease for which no therapeutic action is indicated. However, some patients with moderate mixed disease develop symptoms that stem from their valve disease. Formerly, the argument was raised that if there were no AR, the aortic jet velocity and gradient would be correspondingly lower and would not meet the definitions for severe AS, and obviously there would be only moderate AR by definition. Therefore, no action was recommended. However, recent data suggest that the natural history of moderate mixed disease behaves similarly to that of pure severe AS^{1,2} and that moderate mixed disease has a mortality risk similar to that of pure severe AS. Thus, valve replacement is warranted for the symptomatic patient if the patient's data fulfill any of the criteria for severe AS. The decision about whether to proceed with TAVI versus SAVR is discussed in Section 3.2.4.2.
- For patients with mixed moderate AS/AR who have developed LV dysfunction, as evidenced by an LVEF of $< 50\%$, and who have no other reason for LV dysfunction, valve disease is presumed to be the cause. In such patients, SAVR is indicated.^{1,2}

10.2.2. Intervention for Mixed AS and MR

Patients with combined AS and MR present a difficult and complex decision-making process. There are many potential different scenarios and nuances involved to arrive at the optimal approach for an individual patient, which needs to be made by an MDT with shared decision-making with the patient. Overall, patients with severe AS and severe primary MR

are best treated with SAVR and mitral valve surgery unless the surgical risk is high or prohibitive. If there is a high or prohibitive surgical risk, a staged procedure, with TAVI followed by mitral TEER, can be effective. If there is severe AS and severe secondary MR, either SAVR and mitral valve surgery or a staged approach with TAVI followed by mitral TEER are options. Because there are limited data to support COR, the writing committee has created a table that provides the reader with a perspective on possible interventions in these complex patients (Table 21). Evaluating the short- and long-term outcomes of these approaches will be important.

These proposed procedures are based on the following:

- Many patients with AS also have significant MR that is attributable to either organic (primary) causes or LV remodeling (secondary MR). AVR for AS reduces LV pressure, thereby reducing the pressure gradient that propels volume across the incompetent mitral valve. Although it is reasonable to expect that AVR would reduce MR by reducing LV systolic pressure, this fails to occur in many cases. Not surprisingly, primary MR is more likely to persist after AVR than is secondary MR because AVR does not correct intrinsic mitral valve disease.¹⁻⁵ Therefore, in patients with both AS and MR who are at a low or intermediate surgical risk, it is reasonable to address both valves with surgery. This is particularly true if the mitral valve can be repaired.¹
- For patients with both AS and severe primary MR in whom the mitral valve cannot be repaired, a decision about treatment of the MR will need to be made by the MDT, taking into consideration multiple factors, including the additive risk of a mitral valve replacement. Mitral TEER at a later date may be an option but is likely to have a suboptimal result if the valve cannot be surgically repaired. Thus, double valve replacement with both AVR and mitral valve replacement would be an option if they can be performed at an acceptable level of risk, given that the outcome of the MR after AVR is uncertain.
- Patients with severe AS who are at high to prohibitive surgical risk are best served by TAVI. As noted previously, primary MR may not improve after AVR.²⁻⁵ If symptoms persist after TAVI and if there is suitable anatomy, percutaneous mitral repair can be performed, which can reduce MR and improve symptoms.⁶
- For patients with AS who have secondary MR, the fate of MR after SAVR or TAVI is uncertain.^{2-5,7-10} Although secondary MR is more likely to improve after AVR than is MR attributable to primary mitral valve disease, secondary MR does not improve or may even worsen after AVR in many cases.⁷⁻¹⁰ The mechanism by which reduction in LV pressure after

Table 21. AS/MR Mixed Valve Disease

Severe AS	Severe MR	Surgical Risk	Procedure
SAVR candidate	Primary MR Repairable valve	Low intermediate	SAVR Surgical mitral valve repair
SAVR candidate	Primary MR Valve not repairable	Low intermediate	SAVR Surgical mitral valve replacement
TAVI candidate	Primary Repairable valve	High prohibitive	TAVI Mitral TEER*
SAVR candidate TAVI candidate	Secondary MR	Low intermediate	SAVR Surgical mitral valve repair/mitral valve replacement or TAVI Mitral TEER*
TAVI candidate	Secondary MR	High prohibitive	TAVI Mitral TEER*

*Consider TEER as a later staged procedure if symptoms and severe MR persist after treatment of the AS.

AS indicates aortic stenosis; MR, mitral regurgitation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; and TEER, transcatheter edge-to-edge repair.

AVR does not reduce secondary MR is unknown. With SAVR, the mitral valve can be inspected and addressed, unlike with TAVI, where the mitral valve is left untreated. An alternative approach to patients with AS and secondary MR is to perform TAVI first, and if symptoms remain with persistent severe MR, mitral TEER can be performed if there is suitable anatomy.⁶ The transcatheter approach would be preferred if the patient is at high to prohibitive surgical risk.

10.2.3. Intervention for Mixed MS and MR

Mixed MS and MR often occurs in patients with rheumatic valve disease. Occasionally, mixed MS/MR can occur in patients with severe mitral annular calcification. Asymptomatic mixed disease may be benign because MS protects the LV from the severe volume overload of pure MR. However, if symptoms attributable to mixed mitral disease occur, they are likely because of increased LA pressure from combined increased LA inflow from MR and obstruction to outflow from the LA. An enlarged LA, a high transmitral gradient, or direct measurement of a high LA or pulmonary artery wedge pressure suggest a valvular basis for the patient's symptoms. In such cases, mitral valve replacement may be necessary if therapy with diuretics do not relieve symptoms, but it should be performed only in patients who have severe limiting symptoms.

10.2.4. Intervention for Mixed MS and AR

Combined MS and AR usually result from rheumatic heart disease. When they occur concomitantly, MS is usually the more severe lesion. However, because MS

limits LV filling, it may reduce the stroke volume presented to the aortic valve, in turn reducing the apparent severity of AR.^{1,2} Furthermore, MS reduces the LV cavity size for any degree of AR, causing further potential underestimation of AR severity. In this regard, contrast aortography visualizes AR flow, instead of the echocardiographic visualization of AR velocity of flow, and may be helpful, as is precise assessment of AR regurgitant fraction. In patients who have continued severe symptoms not responsive to diuretics, intervention with valve surgery should be pursued. If mitral anatomy is favorable, options are PMBC to treat the MS, followed by AVR or SAVR and open mitral commissurotomy. In this way, the increased mortality risk of double valve replacement is avoided.³

10.2.5. Intervention for Mixed MS and AS

Almost always the product of rheumatic heart disease, the combination of MS and AS can be very confusing to the clinician. When either lesion is severe, it may limit cardiac output, resulting in reduced flow to the other valve, which reduces transvalvular gradient, leading to underestimation of lesion severity. Echocardiography and invasive hemodynamics are usually necessary to fully assess the severity of each lesion and to decide on appropriate intervention.

11. PROSTHETIC VALVES

11.1. Evaluation and Selection of Prosthetic Valves

11.1.1. Diagnosis and Follow-Up of Prosthetic Valves

Recommendations for Diagnosis and Follow-Up of Prosthetic Valves
Referenced studies that support the recommendations are summarized in Online Data Supplement 38.

COR	LOE	Recommendations
1	B-NR	1. In patients with a surgical or transcatheter prosthetic valve and in patients who have had valve repair, an initial postprocedural TTE study is recommended for evaluation of valve hemodynamics and ventricular function. ¹⁻⁴
1	C-EO	2. In patients with a prosthetic valve or prior valve repair and a change in clinical symptoms or signs suggesting valve dysfunction, repeat TTE is recommended.
1	C-LD	3. In patients with a prosthetic valve replacement or prior valve repair and clinical symptoms or signs that suggest prosthetic valve dysfunction, additional imaging with TEE, gated cardiac CT, or fluoroscopy is recommended, even if TTE does not show valve dysfunction.
2a	C-LD	4. In patients with a bioprosthetic surgical valve, TTE at 5 and 10 years and then annually after implantation is reasonable, even in the absence of a change in clinical status.
2a	C-LD	5. In patients with a bioprosthetic TAVI, TTE annually is reasonable.

Synopsis

The clinical course of patients with prosthetic heart valves or repaired native valves is influenced by several factors, including ventricular function, AF, pulmonary hypertension, and CAD, as well as by the development of valve-related complications. The interval between routine follow-up visits depends on the patient's valve type, the presence of residual heart disease, and other clinical factors. Attention to optimal dental care and endocarditis prophylaxis and any needed anticoagulation is a requisite component of care.

TTE is the primary imaging modality for postoperative assessment of prosthetic valve or repaired native valve function. In the absence of early complications, the index study is performed during hospitalization or within the first several weeks thereafter, depending on individual patient circumstances and the type of valve procedure. Additional imaging, such as TEE, cardiac CT, or fluoroscopy, may be required when valve dysfunction is suspected and in the context of the clinical presentation. A schedule for surveillance TTE studies has become an established feature of long-term follow-up, although the frequency of routine studies that are performed in the absence of clinical change will vary as a function of valve type.

Recommendation-Specific Supportive Text

1. TTE after valve implantation or repair provides an assessment of the procedural results and serves as a baseline against which comparison can be made for any change. TTE provides accurate measurements of transvalvular velocities and pressure gradients, as well as detection and quantitation of transvalvular and paravalvular leak.¹⁻⁴ Normal transvalvular velocities and gradients vary across different types and sizes of prosthetic valves but are also affected by patient-specific factors, including body size and cardiac output. The postoperative study, recorded when the patient is asymptomatic and in a stable hemodynamic state, provides Doppler flow data for a specific valve in an individual patient. In addition, TTE provides assessment of other valve disease(s), pulmonary artery pressure, atrial size, LV and RV size and function, and pericardial disease.
2. Bioprosthetic or repaired native valve dysfunction typically presents with the insidious onset of HF symptoms or a change in the auscultatory findings. More abrupt and severe symptoms may occur with infective endocarditis or rupture of a valve cusp. Patients with mechanical valve dysfunction may present with HF, shock, thromboembolic events, hemolysis, or a change in auscultatory findings. Presentation may often be

acute or subacute because of thrombus formation and more abrupt impairment of leaflet opening or closure. Attention should be directed to the trend in recent INR determinations. Prosthesis-patient mismatch and functional stenosis of a repaired native valve are also to be considered in the evaluation of patients with HF symptoms. Repeat noninvasive assessment begins with transthoracic echocardiography, comparison with the index postoperative study when available, and the use of other modalities as dictated by the clinical context and preliminary findings.

3. TTE is the preferred approach for initial assessment of suspected prosthetic valve dysfunction because it allows for measurement of transvalvular velocity, gradient, and valve area. TTE also allows quantitation of LV volumes and LVEF, an estimate of pulmonary artery systolic pressure, and evaluation of right heart function. However, the LA side of a prosthetic mitral valve is obscured by acoustic shadowing from the TTE approach, resulting in reduced sensitivity for detection of prosthetic MR and prosthetic mitral valve thrombus, pannus, or vegetation. TEE provides superior imaging of the LA side of the mitral prosthesis and is accurate for diagnosis of prosthetic mitral valve dysfunction.^{5,6} Both TTE and TEE are also needed for patients with prosthetic aortic valves in whom the posterior aspect of the valve is shadowed on the TTE approach and the anterior aspect of the valve is shadowed on the TEE approach.^{7,8} TEE has superior sensitivity for the detection of vegetations and abscess formation in patients with suspected prosthetic valve (or annuloplasty ring) endocarditis. With mechanical valve obstruction, fluoroscopy or CT imaging can also be helpful for detection of reduced motion caused by pannus ingrowth or thrombus.
4. Studies based on TTE follow-up estimate that approximately 30% of patients with a surgical aortic valve bioprosthesis develop evidence of valve dysfunction over the 10 years after implantation (defined as an increase in mean gradient of ≥ 10 mm Hg or a worsening of transprosthetic regurgitation from mild to moderate or from moderate to severe).⁹ The incidence of clinically important structural valve deterioration increases markedly more than 10 years after surgery, such that routine annual TTE studies thereafter are reasonable.^{10,11} Risk factors associated with accelerated (<5 years) valve deterioration include young age (<60 years) at implantation, smoking, diabetes mellitus, chronic kidney disease, initial mean gradient ≥ 15 mm Hg, and valve type.^{9,12} The selective adoption of an earlier, annual TTE screening program may be considered for at-risk patients on an individual basis, as up to 13% of patients

with a surgical aortic valve develop hemodynamic valve dysfunction at a median of 6.7 to 9.9 years after implantation.¹² Patients typically remain asymptomatic until valve dysfunction is severe enough to result in adverse hemodynamic consequences or AF. Depending on the valve type and mechanism of regurgitation, some patients with asymptomatic, significant prosthetic valve regurgitation may require reintervention. For example, if prosthetic regurgitation is attributable to a bioprosthetic leaflet tear, more severe acute regurgitation may occur suddenly and cause clinical decompensation. With prosthetic valve stenosis, TTE diagnosis while the patient is asymptomatic alerts the clinician to the need for more frequent follow-up. A standardized definition and grading system for structural valve deterioration for surgical and transcatheter aortic valves have been proposed.¹³ In patients with mechanical valve prostheses, routine annual TTE evaluation is not needed if the postoperative baseline study is normal and no clinical change is apparent. Many of these patients require TTE studies for other indications, however, such as for the assessment of LV function, pulmonary artery pressure, or other cardiac or valve disease.

5. Durability data for bioprosthetic TAVI valves are less robust than the data for surgically implanted bioprosthetic valves. To date, the intermediate-term durability of TAVI valves has compared favorably with that of SAVR valves, as reported in randomized trials and registries.^{14–21} For the most part, these data reflect observations made in older patients and may not be applicable to younger populations (eg, <70 years). TAVI-based protocols typically include routine TTE before discharge and at 30 days and 1 year, in part because of reporting requirements. In the absence of clinical change, routine annual TTE studies are reasonable as experience continues to accumulate.

11.1.2. Selection of Prosthetic Valve Type: Bioprosthetic Versus Mechanical Valve

Recommendations for Prosthetic Valve Type: Bioprosthetic Versus Mechanical Valve		
Referenced studies that support the recommendations are summarized in Online Data Supplement 35.		
COR	LOE	Recommendations
1	C-LD	1. For patients who require heart valve replacement, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and risks of anticoagulant therapy and the potential need for and risks associated with valve reintervention.

Recommendations for Prosthetic Valve Type: Bioprosthetic Versus Mechanical Valve (Continued)		
COR	LOE	Recommendations
1	C-EO	2. For patients of any age requiring valve replacement for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic valve is recommended.
2a	B-NR	3. For patients <50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve. ¹
2a	B-NR	4. For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR, with consideration of individual patient factors and after informed shared decision-making. ^{1–10}
2a	B-NR	5. In patients >65 years of age who require AVR, it is reasonable to choose a bioprosthesis over a mechanical valve. ¹
2a	B-NR	6. For patients <65 years of age who have an indication for mitral valve replacement, do not have a contraindication to anticoagulation, and are unable to undergo mitral valve repair, it is reasonable to choose a mechanical mitral prosthesis over a bioprosthetic valve. ^{1,7,10,11}
2a	B-NR	7. For patients ≥65 years of age who require mitral valve replacement and are unable to undergo mitral valve repair, it is reasonable to choose a bioprosthesis over a mechanical valve. ^{1,7,11}
2b	B-NR	8. In patients <50 years of age who prefer a bioprosthetic AVR and have appropriate anatomy, replacement of the aortic valve by a pulmonic autograft (the Ross procedure) may be considered at a Comprehensive Valve Center. ^{12–14}

Synopsis

Shared decision-making about the choice of prosthetic valve type is influenced by several factors, including patient age, values, and preferences; expected bioprosthetic valve durability, avoidance of patient–prosthesis mismatch, and the potential need for and timing of reintervention; and the risks associated with long-term VKA anticoagulation after a mechanical valve replacement. (See also Section 3.2.4 regarding valve choice in patients with AS.) Despite the significantly higher rate of bioprosthetic structural valve deterioration observed in younger versus older patients,^{7–12,15} many younger patients choose to avoid a mechanical prosthesis because they are unwilling to consider long-term VKA therapy because of the inconvenience of monitoring, dietary restrictions, medication interactions, and the need to restrict participation in some types of athletic activity. A mechanical valve might be a prudent choice for patients for whom a second surgical procedure would be very high risk (eg, those with prior radiation exposure). The availability of TAVI has changed

the dynamics of the discussion of the trade-offs between mechanical and bioprosthetic valves in younger patients (Table 22) (Figure 11).^{16–19}

Recommendation-Specific Supportive Text

1. The choice of valve prosthesis in each patient is based on consideration of several factors, including valve durability, expected hemodynamics for valve type and size, surgical or interventional risk, the potential need for long-term anticoagulation, and patient values and preferences. The trade-off between the risk of reintervention for bioprosthetic valve deterioration and the risk of long-term anticoagulation should be discussed. Some patients prefer to avoid repeat surgery and are willing to accept the risks and inconvenience of lifelong anticoagulant therapy. Other patients are unwilling to consider long-term anticoagulation because of the inconvenience of monitoring, the attendant dietary and medication interactions, and the need to restrict participation in some types of physical activity. The incidence of structural deterioration of a bioprosthesis is greater in younger patients, but the risk of bleeding from anticoagulation is higher in older patients. In patients with shortened longevity or multiple comorbidities, a bioprosthesis might be more appropriate. In women who desire subsequent pregnancy, the issue of anticoagulation during pregnancy is an additional consideration (see pregnancy-related issues in Section 13.5).^{20,21}
2. Anticoagulant therapy with VKA is necessary in all patients with a mechanical valve to prevent valve thrombosis and thromboembolic events. If anticoagulation is contraindicated or if the patient refuses VKA therapy, an alternative valve choice is appropriate. Newer anticoagulant agents have not been shown to be safe or effective in patients with mechanical heart valves.
3. Patients <50 years of age at the time of AVR incur a higher and earlier risk of bioprosthetic valve deterioration.^{4,10,11,22–24} Overall, the predicted 15-year risk of needing reoperation because of structural deterioration is 22% for patients 50 years of age, 30% for patients 40 years of age, and 50% for patients 20 years of age, although it is recognized that all bioprostheses are not alike in terms of durability.¹¹ Anticoagulation with a VKA can be accomplished with acceptable risk in most patients <50 years of age, particularly in compliant patients with appropriate monitoring of INR levels. Thus, the balance between valve durability and risk of bleeding and thromboembolic events favors the choice of a mechanical valve in patients <50

Table 22. Selected Factors That May Impact Shared Decision-Making for the Choice of Prosthetic Valve

Favor Mechanical Prosthesis	Favor Bioprosthesis
Age <50 y Increased incidence of structural deterioration with bioprosthesis (15-y risk: 30% for age 40 y, 50% for age 20 y) Lower risk of anticoagulation complications	Age >65 y Low incidence of structural deterioration (15-y risk: <10% for age >70 y) Higher risk of anticoagulation complications
Patient preference (avoid risk of reintervention)	Patient preference (avoid risk and inconvenience of anticoagulation)
Low risk of long-term anticoagulation	High risk of long-term anticoagulation
Compliant patient with either home monitoring or close access to INR monitoring	Limited access to medical care or inability to regulate VKA
Other indication for long-term anticoagulation (eg, AF)	Access to surgical centers with low reoperation mortality rate
High-risk reintervention (eg, porcelain aorta, prior radiation therapy)	Access to transcatheter ViV replacement
Small aortic root size for AVR (may preclude ViV procedure in future)	TAVI valves have larger effective orifice areas for smaller valve sizes (avoid patient–prosthesis mismatch)

AF indicates atrial fibrillation; AVR, aortic valve replacement; INR, international normalized ratio; TAVI, transcatheter aortic valve implantation; ViV, valve-in-valve; and VKA, vitamin K antagonist.

years of age, unless anticoagulation is not desired, cannot be monitored, or is contraindicated.

4. Uncertainty and debate continue about which type of AVR is appropriate for patients 50 to 65 years of age. Newer surgical bioprosthetic valves may show greater freedom from structural deterioration, specifically in the older individual, although a high late mortality rate in these studies may preclude recognition of valve dysfunction.^{11,15–19} The risks of bleeding and thromboembolism with mechanical prostheses are low, especially in compliant patients with appropriate INR monitoring. Several studies have shown a survival advantage with a mechanical prosthesis in this age group. Alternatively, large retrospective observational studies have shown similar long-term survival rates in patients 50 to 69 years of age undergoing mechanical versus bioprosthetic valve replacement.^{22–24} In general, patients with mechanical valves experience a higher risk of bleeding because of anticoagulation, whereas individuals who receive bioprosthetic valves experience a higher rate of reoperation attributable to structural deterioration of the prosthesis, as well as perhaps a decrease in survival rate.^{6,25–27} Several other factors should be considered in the choice of type of valve prosthesis (see Section 11.1). Ultimately, the choice of mechanical versus

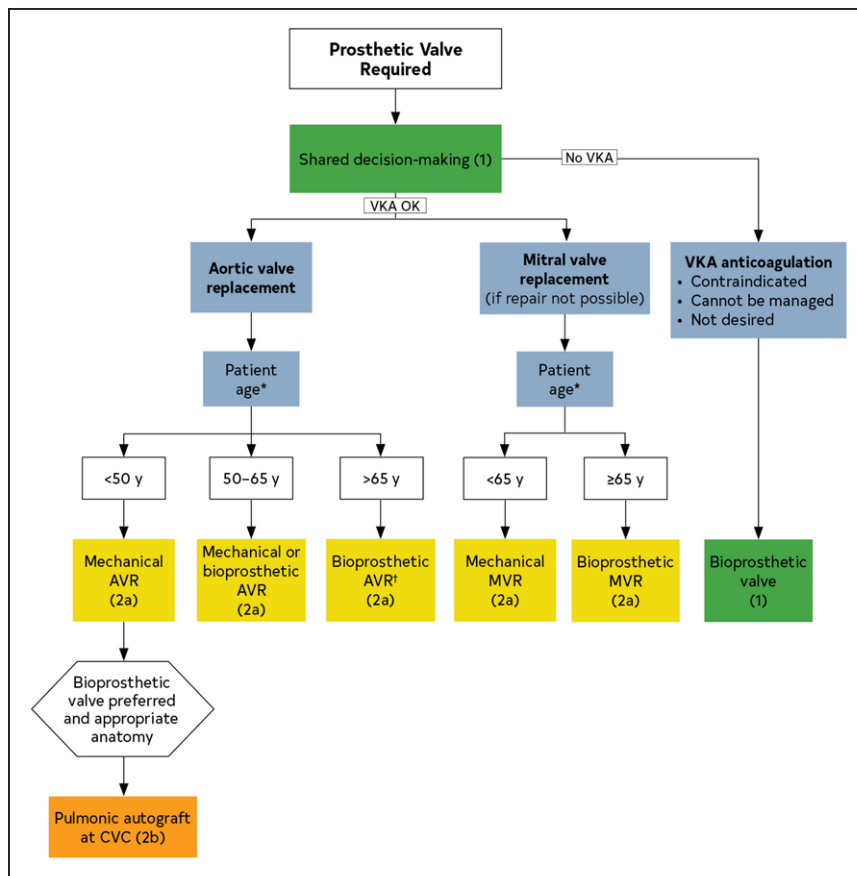


Figure 11. Prosthetic valves: choice of bioprosthetic versus mechanical valve type.

Colors correspond to Table 2. *Approximate ages, based on US Actuarial Life Expectancy tables, are provided for guidance. The balance between expected patient longevity and valve durability varies continuously across the age range, with more durable valves preferred for patients with a longer life expectancy. Bioprosthetic valve durability is finite (with shorter durability for younger patients), whereas mechanical valves are very durable but require lifelong anticoagulation. Long-term (20-y) data on outcomes with surgical bioprosthetic valves are available; robust data on transcatheter bioprosthetic valves extend to only 5 y, leading to uncertainty about longer-term outcomes. The decision about valve type should be individualized on the basis of patient-specific factors that might affect expected longevity. †See Section 3.2.4.2 for a discussion of the choice of TAVI versus SAVR. AVR indicates aortic valve replacement; CVC, Comprehensive Valve Center; VKA, vitamin K antagonist; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

bioprosthetic valve replacement for all patients, but especially for those between 50 and 65 years of age, should be made in a shared decision-making process that must account for the trade-offs between durability (and the need for reintervention), bleeding, and thromboembolism.¹

- In patients >65 years of age at the time of bioprosthetic AVR, the likelihood of primary structural deterioration at 15 to 20 years is only about 10%.²⁸⁻³¹ In addition, older patients are at higher risk of bleeding complications related to VKA therapy and more often require interruption of VKA therapy for noncardiac surgical and interventional procedures. It is reasonable to use a bioprosthetic valve in patients >65 years of age to avoid the risks of anticoagulation because the durability of the valve exceeds the expected years of life.
- In general, patients with mechanical valve replacement experience a higher risk of bleeding because of anticoagulation, whereas individuals who receive a bioprosthetic valve replacement incur a higher risk of repeat intervention attributable to structural valve deterioration. In patients <65 years of age, observational data suggest better long-term outcomes with a mechanical mitral valve replacement, even when the risks and inconvenience of long-term VKA anticoagulation are considered. In

a propensity-matched analysis from New York's Statewide Planning and Research Cooperative System (SPARCS), although there was no survival difference for patients 50 to 69 years of age undergoing mechanical versus bioprosthetic mitral valve replacement,⁷ the rates of reoperation were lower (HR: 0.59) with a mechanical valve, though stroke risk (HR: 1.62) was higher. In the 2017 report from the California Office of Statewide Health Planning and Development,¹ for patients who underwent mitral-valve replacement and were 40 to 69 years of age, receipt of a biological prosthesis was associated with a mortality rate significantly higher than that seen with receipt of a mechanical prosthesis.¹ The choice of a mechanical mitral valve in patients <65 years of age who are good candidates for anticoagulation should account for these observational, nonrandomized data and abide by the principles of shared decision-making.^{1,7,10}

- Hazards associated with anticoagulation increase with age, and rates of structural valve deterioration decline significantly. In patients >65 years of age, the ratio of valve durability to life expectancy supports the use of a bioprosthetic mitral valve replacement, which allows avoidance of the risks of long-term VKA anticoagulation in these older patients. In 1

observational study, the expected durability of a bioprosthetic mitral valve replacement was 11.4 years in patients <60 years of age, 16.6 years in those 60 to 70 years of age, and 19.4 years in those >70 years of age.¹¹ In the 2017 report from the California Office of Statewide Health Planning and Development,¹ overall survival rates were similar for patients 70 to 79 years of age who underwent mechanical versus bioprosthetic mitral valve replacement, and bleeding risk was lower with a bioprosthetic valve.¹

8. Replacement of the aortic valve with a pulmonary autograft (the Ross procedure) is a complex operation involving replacement of the aortic valve by the patient's own pulmonic valve, along with placement of a pulmonic valve homograft. The Ross procedure allows the patient to avoid a prosthetic heart valve and the risks of anticoagulation, and it provides excellent valve hemodynamics. However, both the pulmonic homograft in the pulmonic position and the pulmonary autograft (the neo-aortic valve) are at risk of valve degeneration. The failure of the Ross procedure is most often attributable to regurgitation of the neo-aortic valve in the second decade after the operation. In addition, at least half of pulmonic homograft valves require reintervention within 10 to 20 years. Calcification of the homograft and adhesions between the homograft and neo-aorta may increase the difficulty of reoperation. The Ross procedure typically is reserved for younger patients with appropriate anatomy and tissue characteristics in whom anticoagulation is either contraindicated or undesirable, and it is performed only at Comprehensive Valve Centers by surgeons experienced in this procedure.^{12–14,32}

11.2. Antithrombotic Therapy

Recommendations for Antithrombotic Therapy for Prosthetic Valves		
Referenced studies that support the recommendations are summarized in Online Data Supplement 38.		
COR	LOE	Recommendations
1	A	1. In patients with a mechanical prosthetic valve, anticoagulation with a VKA is recommended. ^{1–5}
1	B-NR	2. For patients with a mechanical bileaflet or current-generation single-tilting disk AVR and no risk factors for thromboembolism, anticoagulation with a VKA to achieve an INR of 2.5 is recommended. ^{6–8}
1	B-NR	3. For patients with a mechanical AVR and additional risk factors for thromboembolism (eg, AF, previous thromboembolism, LV dysfunction, hypercoagulable state) or an older-generation prosthesis (eg, ball-in-cage), anticoagulation with a VKA is indicated to achieve an INR of 3.0. ^{9,10}

Recommendations for Antithrombotic Therapy for Prosthetic Valves (Continued)		
COR	LOE	Recommendations
1	B-NR	4. For patients with a mechanical mitral valve replacement, anticoagulation with a VKA is indicated to achieve an INR of 3.0. ^{9,11}
2a	B-R	5. For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants. ^{12–14}
2a	B-NR	6. For all patients with a bioprosthetic SAVR or mitral valve replacement, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants. ^{9,15–18}
2a	B-NR	7. For patients with a bioprosthetic SAVR or mitral valve replacement who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical replacement. ^{15,19–25}
2b	B-R	8. For patients with a mechanical SAVR or mitral valve replacement who are managed with a VKA and have an indication for antiplatelet therapy, addition of aspirin 75 to 100 mg daily may be considered when the risk of bleeding is low. ²⁶
2b	B-R	9. For patients with a mechanical On-X AVR and no thromboembolic risk factors, use of a VKA targeted to a lower INR (1.5–2.0) may be reasonable starting ≥3 months after surgery, with continuation of aspirin 75 to 100 mg daily. ^{27,28}
2b	B-NR	10. For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual-antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation. ^{12,13,29}
2b	B-NR	11. For patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation. ^{23,31–33}
3: Harm	B-R	12. For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated in the absence of other indications for oral anticoagulants. ³⁰
3: Harm	B-R	13. For patients with a mechanical valve prosthesis, anticoagulation with the direct thrombin inhibitor, dabigatran, is contraindicated. ^{4,5}
3: Harm	C-EO	14. For patients with a mechanical valve prosthesis, the use of anti-Xa direct oral anticoagulants has not been assessed and is not recommended. ^{34–37}

Synopsis

Antithrombotic therapy after prosthetic valve implantation is provided to prevent valve/leaflet thrombosis and reduce the incidence of thromboembolic complications. The use of any strategy must be balanced against the risk of bleeding. VKAs remain the cornerstone of therapy

for patients with mechanical valve prostheses. Oral anti-thrombin and anti-Xa agents are not approved for use in these patients. The addition of mono- or dual-antiplatelet therapy to VKA treatment for other indications (eg, acute coronary syndrome or percutaneous coronary intervention [PCI]) must be done with caution. The evidence base for the optimal antithrombotic strategy across subgroups of patients who have received a bioprosthetic valve is not robust. Practice patterns around the use of antiplatelet and anticoagulant medications in these patients vary as a function of method of implantation (surgical versus transcatheter), the presence of any independent indication for anticoagulation (eg, AF, venous thromboembolic disease), and local/institutional care pathways (Figure 12).

Recommendation-Specific Supportive Text

1. All patients with mechanical valves require life-long anticoagulant therapy with a VKA.^{1–5} In addition to the thrombogenicity of the intravascular prosthetic material, mechanical valves impose abnormal flow conditions, with zones of low flow within their components, as well as areas of high-shear stress, which can cause platelet activation that leads to valve thrombosis and embolic events. Therapy with an oral VKA at an INR goal appropriate for the comorbidity of the patient and the type and position of the mechanical valve prosthesis is required to decrease the incidence of thromboembolism and associated morbidity. Data show that anticoagulation with a VKA is protective against valve thrombosis (OR: 0.11; 95% CI: 0.07–0.2) and thromboembolic events (OR: 0.21; 95% CI: 0.16–0.27). It is preferable to specify a single INR target for each patient and to recognize that the acceptable range includes 0.5 INR units on each side of this target. A specific target is preferable because it reduces the likelihood of patients having INR values consistently near the upper or lower boundary of the range. Fluctuations in INR are associated with an increased incidence of complications in patients with prosthetic heart valves.^{19,38}
2. The rate of thromboembolism in patients with a bileaflet mechanical AVR treated with a VKA is estimated to be 0.53% per patient-year over the INR range of 2.0 to 4.5. In a large retrospective study, adverse events increased if the INR was >4.0 in patients with a mechanical AVR. In patients with a current-generation mechanical AVR without other risk factors for thromboembolism, in the group treated to an INR of 2.0 to 3.0, the risk of thromboembolic events was similar to, but the risk of bleeding lower than, those of the group treated to an INR of 3.0 to 4.5 ($P<0.01$).⁷ In a randomized trial comparing moderate-intensity (INR 2.0–3.0) with high-intensity (INR 3.0 to 4.5) oral anticoagulation in patients with a single mechanical valve replacement, there was no difference in embolic events but a reduction in bleeding with the moderate-intensity group.⁸ In a study comparing an INR target of 1.5 to 2.5 with a target of 2.0 to 3.0 in patients with current-generation mechanical aortic prosthetic valves and no other thromboembolic risk factors, the lower INR target range was noninferior, but the quality of the evidence was low.⁶ For current-generation mechanical valve prostheses in the aortic position, an INR of 2.5 (range, 2.0–3.0) provides a reasonable balance between the risks of thromboembolism and bleeding.^{8,9}
3. In patients with an aortic mechanical prosthesis who are at higher risk of thromboembolic complications, the INR should be maintained at 3.0 (range, 2.5–3.5). Risk factors include AF, previous thromboembolism, hypercoagulable state, and older-generation prosthesis (eg, ball-in-cage).¹⁰ Severe LV dysfunction may also increase thromboembolic risk.⁹
4. The incidence of thromboembolism is higher with mitral than with aortic mechanical valves, and it is lower in mitral mechanical valve patients with a higher rather than a lower INR. In the GELIA (German Experience with Low Intensity Anticoagulation) study of patients with a mechanical mitral prosthesis, a lower INR range (2.0–3.5) was associated with a lower survival rate than that seen with a higher target INR range (2.5–4.5).¹¹ Patient compliance may be challenging with higher INR goals. In one study, patients with a target INR between 2.0 and 3.5 were within that range 74.5% of the time. In contrast, patients with a target INR of 3.0 to 4.5 were within range only 44.5% of the time. An INR target of 3.0 (range, 2.5–3.5) provides a reasonable balance between the risks of under- or over-anticoagulation in patients with a mechanical mitral valve.⁹
5. Prior recommendations about the use of antiplatelet therapy after TAVI were derived from the protocols used in the pivotal randomized studies showing the safety and effectiveness of this technology. These protocols were in turn adopted from studies of patients undergoing PCI. The small and underpowered ARTE trial (Aspirin Versus Aspirin plus Clopidogrel Following Transcatheter Aortic Valve Implantation) suggested that single-agent therapy, compared with dual-agent therapy, tended to reduce the risk of major adverse events (death, myocardial infarction, stroke, transient ischemic attack, and major or life-threatening bleeding) after TAVI. Whereas there were no

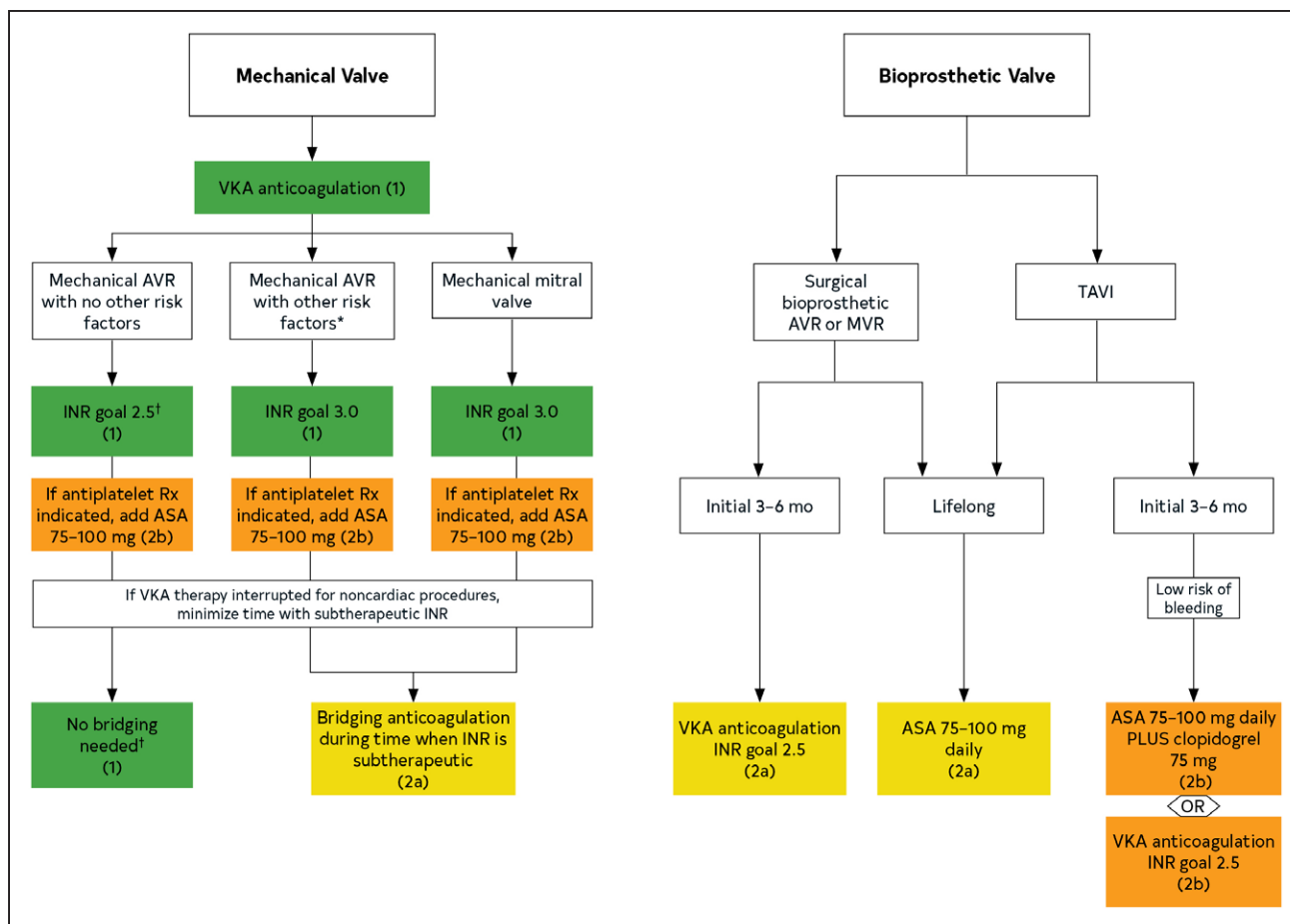


Figure 12. Antithrombotic therapy for prosthetic valves.

Colors correspond to Table 2. *Thromboembolic risk factors include an older-generation valve, AF, previous thromboembolism, hypercoagulable state, and LV systolic dysfunction. †For a mechanical On-X AVR and no thromboembolic risk factors, a goal INR of 1.5–2.0 plus aspirin 75–100 mg daily may be reasonable starting ≥ 3 months after surgery. ASA indicates aspirin; AVR, aortic valve replacement; INR, international normalized ratio; MVR, mitral valve replacement; VKA, vitamin K antagonist; Rx, medication; and TAVI, transcatheter aortic valve implantation.

differences between the groups with respect to death, stroke, or myocardial infarction, dual therapy was associated with a significantly increased risk of major or life-threatening bleeding.¹² A systematic review and meta-analysis comprising approximately 2500 patients suggested that single-agent therapy is associated with fewer 30-day deaths and less major bleeding than is seen with dual-agent therapy.¹³ There are several ongoing trials on this subject.³⁹

- The risk of thromboembolism is approximately 0.7% per year in patients with biological valves in sinus rhythm; Figure 13 is derived from several studies in which most patients were not undergoing therapy with VKA. Among patients with bioprosthetic valves, those with a mitral prosthesis have higher rates of thromboembolism than do those with an aortic prosthesis (2.4% per patient-year versus 1.9% per patient-year).¹⁵ In studies of patients with bioprosthetic aortic valves who were in sinus rhythm and had no other indications for anticoagulation, the incidence of

thromboembolic events, bleeding, and death was similar in those who received aspirin or aspirin-like antiplatelet agents only and in those who received VKA.^{16,17,19} There are no studies examining the long-term effects of antiplatelet agents in patients with bioprosthetic mitral valve repair or mitral valve repair; the beneficial effects seen with bioprosthetic aortic valves may apply to mitral valves, as well.^{9,18}

- Many patients who undergo surgical implantation of a bioprosthetic mitral or aortic valve will not require lifelong anticoagulation in the absence of an independent indication, such as AF. However, there is an increased risk of ischemic stroke early after operation, particularly in the first 90 to 180 days after either bioprosthetic AVR or mitral valve replacement.^{5,24,31,34–37,40} Anticoagulation early after valve implantation is intended to decrease the risk of thromboembolism until the prosthetic valve is fully endothelialized. The potential benefit of anticoagulation therapy must be weighed against the risk of bleeding. In a nonrandomized

study, patients with a bioprosthetic mitral valve replacement who received anticoagulation had a lower rate of thromboembolism than that of those who did not receive therapy with VKA.¹⁵ Even with routine anticoagulation early after mitral valve surgery, the incidence of ischemic stroke within the first 30 postoperative days was higher after replacement with a biological prosthesis than after mitral valve repair ($1.5\% \pm 0.4\%$) or replacement with a mechanical prosthesis.²¹ Small studies have not established a convincing net benefit of anticoagulation after implantation of a bioprosthetic AVR^{24,25}; however, a large observational Danish registry demonstrated a lower risk of stroke and death with VKA, which extended up to 6 months, without a significantly increased bleeding risk.²⁰ Concern has been raised about the incidence of subclinical bioprosthetic valve leaflet thrombosis after surgical valve replacement.¹⁹ In addition, the PARTNER 2 (Placement of Aortic Transcatheter Valves) investigators reported that the use of anticoagulation after bioprosthetic AVR in intermediate- or higher-surgical risk patients was safe and associated with a significant reduction in 6-month stroke rates.²³ Ninety-five percent of the anticoagulated patients in this registry were discharged on warfarin in preference to a direct oral anticoagulant.

8. The prior recommendation to add low-dose aspirin to therapeutic VKA therapy for a mechanical valve prosthesis was based on studies performed decades ago that included many patients with older-generation prostheses who also had additional thromboembolic and vascular risk factors. A 2013 Cochrane Systematic Review showed that compared with anticoagulation alone, the addition of an antiplatelet agent reduced the risk of thromboembolic events and the total mortality rate but at the cost of an increased and offsetting risk of major bleeding.²⁶ The authors pointed out that the quality of the included trials tended to be low, possibly reflecting the era when most trials were conducted. An individualized approach that takes the risk of bleeding into account is required.
9. In patients without risk factors who receive a mechanical On-X aortic heart valve (On-X Life Technologies Inc., Austin, Texas), targeting the INR to a lower goal (1.5–2.0) in conjunction with aspirin 81 mg daily may be a strategy for long-term management. Warfarin dosing is targeted to an INR of 2.5 (range, 2.0–3.0) for the first 3 months after surgery, during which low-dose aspirin is also used.²⁷ This recommendation is based on a single RCT²⁷ of lower- versus standard-intensity VKA therapy (with low-dose

aspirin) in patients undergoing On-X AVR. The lower-intensity INR group experienced significantly less major and minor bleeding, whereas the rates of stroke, transient ischemic attack, total neurological events, and all-cause mortality were similar between the 2 groups. A subsequent publication from these investigators showed harm with a strategy of dual-antiplatelet therapy versus low-intensity anticoagulation plus low-dose aspirin.²⁸

10. The routine use of dual-antiplatelet therapy for 6 months after TAVI, which has been the default strategy since the introduction of this technology into clinical use, has been not been rigorously assessed (see previous discussion). There are several ongoing trials evaluating antithrombotic strategies after TAVI. A small, single-center RCT of patients receiving a self-expanding TAVI device showed no difference in a composite endpoint of major adverse cardiac and cerebrovascular events or life-threatening bleeding with aspirin plus clopidogrel versus aspirin alone at 30 days and 6 months.²⁹ Compared with single-agent therapy, dual-antiplatelet therapy may be associated with a higher risk of bleeding and no significant difference in rates of valve leaflet thrombosis, thromboembolism, or valve performance.^{12,13} Other procedural and patient factors may impact the decision to use dual-antiplatelet therapy.
11. The selective use of VKA therapy might be considered after TAVI in patients at low bleeding risk on an individual basis. The PARTNER 2 investigators reported that the use of an anticoagulant (95% warfarin) after TAVI in intermediate- or higher-surgical risk patients was associated with a lower incidence of an increase in mean gradient >10 mmHg over the first year after implantation.²³ This Doppler finding may reflect the development of leaflet thrombosis, for which a change in the frequency of follow-up examinations or treatment could be considered. VKAs may be more effective than direct oral anticoagulants for reduction of death, myocardial infarction, and cerebrovascular events in patients undergoing TAVI with an indication for anticoagulation.³³ The selective short-term use of VKAs after ViV TAVI is predicated on the observation that valve thrombosis may be more frequent in this patient population.³²
12. The GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial assessed a strategy of low-dose rivaroxaban (10 mg daily) plus low-dose aspirin (75–100 mg daily) versus an antiplatelet strategy

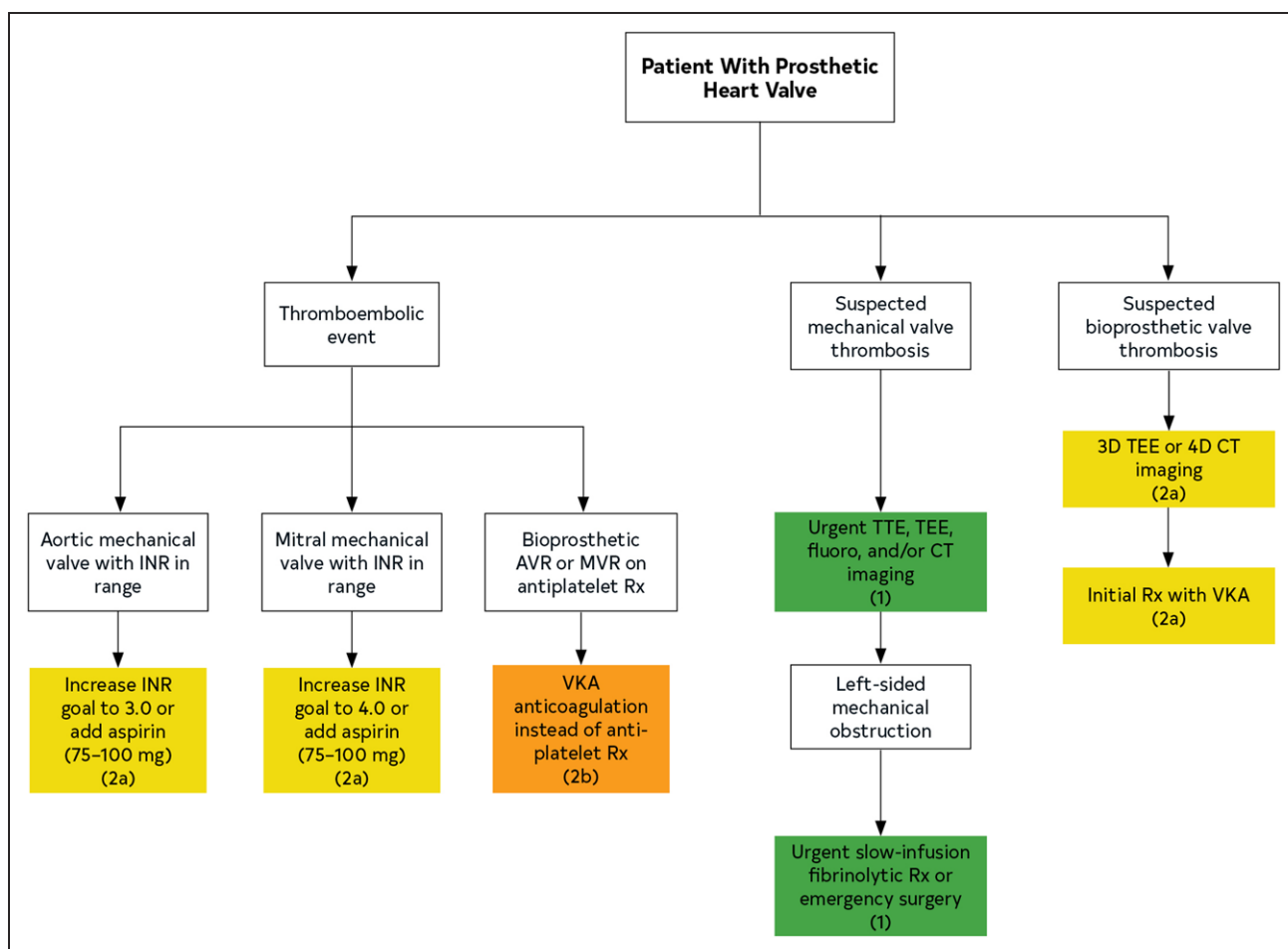


Figure 13. Management of embolic events and valve thrombosis.

Colors correspond to Table 2. 3D indicates 3-dimensional; 4D, 4-dimensional; AVR, aortic valve replacement; CT, computed tomography; INR, international normalized ratio; MVR, mitral valve replacement; Rx, medication; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and VKA, vitamin K antagonist.

of low-dose aspirin plus clopidogrel (75 mg daily). The study was terminated prematurely by the Data and Safety Monitoring Board because of safety concerns. The rivaroxaban strategy was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than those seen with the antiplatelet-based strategy.³⁰

13. Dabigatran was compared with warfarin in the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients after Heart Valve Replacement) trial. It was stopped prematurely for excessive thrombotic and bleeding complications in the dabigatran arm.^{4,5}
14. The safety and efficacy of conventional-dose oral anti-Xa agents in patients with a mechanical valve prosthesis have not been evaluated.^{33–36}

11.3. Bridging Therapy

Recommendations for Bridging Therapy During Interruption of Oral Anticoagulation in Patients With Prosthetic Heart Valves		
COR	LOE	Recommendations
1	C-EO	1. For patients with mechanical heart valves who are undergoing minor procedures (eg, dental extractions or cataract removal) where bleeding is easily controlled, continuation of VKA anticoagulation with a therapeutic INR is recommended.
1	C-LD	2. For patients with a bileaflet mechanical AVR and no other risk factors for thromboembolism who are undergoing invasive procedures, temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended.
2a	C-LD	3. For patients with a mechanical valve prosthesis receiving VKA therapy who require immediate/emergency noncardiac surgery or an invasive procedure, administration of 4-factor prothrombin complex concentrate (or its activated form) is reasonable.

Recommendations for Bridging Therapy During Interruption of Oral Anticoagulation in Patients With Prosthetic Heart Valves (Continued)		
COR	LOE	Recommendations
2a	C-LD	4. For patients with bioprosthetic heart valves or annuloplasty rings who are receiving anticoagulation for AF, it is reasonable to consider the need for bridging anticoagulant therapy around the time of invasive procedures on the basis of the CHA ₂ DS ₂ -VASc score weighed against the risk of bleeding.
2a	C-LD	5. For patients who are undergoing invasive procedures and have 1) a mechanical AVR and any thromboembolic risk factor, 2) an older-generation mechanical AVR, or 3) a mechanical mitral valve replacement, bridging anticoagulation therapy during the preoperative time interval when the INR is subtherapeutic is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention.

Synopsis

The management of patients with prosthetic heart valves or repaired native valves in whom interruption of anticoagulant therapy is needed for diagnostic or surgical procedures should take into account the type and location of the valve, the type of procedure, thromboembolic risk factors, the length of time over which oral anticoagulation will be withheld, and bleeding risk. “Bridging” therapy with either intravenous unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) has evolved empirically to reduce thromboembolic events during temporary interruption of oral anticoagulation in higher-risk patients, such as those with a mechanical mitral valve replacement or AVR and additional risk factors for thromboembolism.¹

Recommendation-Specific Supportive Text

1. Antithrombotic therapy should not be stopped for procedures in which bleeding is unlikely or would be inconsequential if it occurred (eg, surgery on the skin, dental cleaning, or simple treatment for dental caries). Eye surgery, particularly for cataracts or glaucoma, is usually associated with very little bleeding and thus is frequently performed without alteration of anticoagulation with a VKA.
2. In patients with a bileaflet mechanical AVR and no other risk factors, the risk of thromboembolism after stopping anticoagulation with a VKA is small if the drug is withheld for only a few days. In these low-risk patients, the inconvenience and expense of bridging anticoagulation can be avoided. When it is necessary to interrupt VKA therapy, the agent is stopped 2 to 4 days before the procedure and restarted as soon as bleeding risk allows, typically 24 hours after surgery.^{2,3}

3. In patients with mechanical valves on long-term VKA therapy who require emergency surgery or invasive procedures, anticoagulation can be reversed by administration of intravenous prothrombin complex concentrate. It replaces the coagulation factors that are decreased by VKAs and contains all coagulant factors, including II, VII, IX, and X, in inactivated form. Onset of effect is within 5 to 15 minutes, and duration of effect persists for 12 to 24 hours. With fresh frozen plasma, onset of effect is longer (1–4 hours), and duration of effect is shorter (<6 hours), depending on the dose given. The effect of prothrombin complex concentrate can be prolonged with vitamin K, if indicated.⁴
4. Although the large phase III trials comparing NOACs with warfarin excluded patients with moderate to severe rheumatic MS or mechanical heart valves, some did include patients with other VHD and bioprosthetic valve replacement or repair.⁵ Many patients who develop an indication for anticoagulation late after bioprosthetic heart valve replacement or native valve repair are treated safely with direct oral anticoagulants, as predicated on their CHA₂DS₂-VASc score and the predicted risks of bleeding. Considerations about the need for bridging therapy in these individuals can follow the same strategy applied to other subsets of patients who have AF without moderate to severe rheumatic MS or a mechanical prosthesis.
5. When interruption of oral VKA therapy is deemed necessary, the agent is usually stopped 3 to 4 days before the procedure and is restarted postoperatively as soon as bleeding risk allows. Bridging anticoagulation with intravenous UFH or subcutaneous LMWH is started when the INR falls below the therapeutic threshold (ie, 2.0 or 2.5, depending on the clinical context), usually 36 to 48 hours before surgery, and is stopped 4 to 6 hours (for intravenous UFH) or 12 hours (for subcutaneous LMWH) before the procedure. There are no randomized comparative-effectiveness trials evaluating a strategy of bridging versus no bridging in adequate numbers of patients with prosthetic heart valves who need temporary interruption of oral anticoagulant therapy, although such studies are ongoing. The evidence cited to support bridging therapy derives from cohort studies with poor or no comparator groups.^{1,6–14} In patient groups other than those with mechanical heart valves, increasing concerns have surfaced that bridging therapy exposes patients to higher bleeding risks without reducing the risk of thromboembolism.¹⁵ Accordingly, decisions about bridging should be individualized and should account for the trade-offs between thrombosis and bleeding.

11.4. Excessive Anticoagulation and Serious Bleeding With Prosthetic Valves

Recommendations for Management of Excessive Anticoagulation and Serious Bleeding in Patients With Prosthetic Valves		
Referenced studies that support the recommendations are summarized in Online Data Supplement 37.		
COR	LOE	Recommendations
2a	C-LD	1. For patients with mechanical valves and uncontrollable bleeding who require immediate reversal of anticoagulation, administration of 4-factor prothrombin complex (or its activated form) is reasonable.
2a	C-LD	2. For patients with mechanical valves and uncontrollable bleeding who have received 4-factor prothrombin concentrate complex, adjunctive use of intravenous vitamin K is reasonable if resumption of VKA therapy is not anticipated for 7 days.
2a	B-NR	3. For patients with bioprosthetic valves or annuloplasty rings who are receiving a direct oral anticoagulant and who require immediate reversal of anticoagulation because of uncontrollable bleeding, treatment with idarucizumab (for dabigatran) or andexanet alfa (for anti-Xa agents) is reasonable. ¹⁻⁵
2b	C-LD	4. For patients with a mechanical prosthetic valve and supratherapeutic INR (>5.0) who are not actively bleeding, the benefit of individualized treatment with oral vitamin K, in addition to temporary withdrawal of the VKA, is uncertain.

Synopsis

Excessive VKA anticoagulation greatly increases the risk of hemorrhage. However, a rapid decrease in INR to a subtherapeutic level may increase the risk of thromboembolism.⁶ Nevertheless, for patients who require immediate reversal of VKA anticoagulation because of severe or life-threatening bleeding or the need for an emergency procedure, reversal is indicated.⁷ Preference is placed on the use of rapid-acting and reliable agents, such as prothrombin complex concentrate or its activated form. Addition of vitamin K can be considered on an individual basis.⁸⁻¹³ Specific antidotes are available to reverse the effects of dabigatran (idarucizumab) and the oral anti-Xa (andexanet alfa) anticoagulants.

Recommendation-Specific Supportive Text

1. Four-factor prothrombin complex concentrate includes factors II, VII, IX, and X. Onset of effect is within 5 to 15 minutes, and duration of effect is 12 to 24 hours. It is a more specific and reliable reversal agent than fresh frozen plasma.⁸
2. Vitamin K is a cofactor for hepatic production of factors II, VII, IX, and X. Onset of effect depends on the route of administration (intravenous versus oral), and the dose given should be predicated on the presence of active bleeding, the maintenance dose of the VKA, the magnitude of INR elevation, and the desired range into which to reduce the INR.^{7,9-11}

A 10-mg intravenous dose is recommended for life-threatening bleeding when there is no concern for restarting the VKA within the next week.

3. Idarucizumab (two, 2.5-mg bolus infusions no more than 15 minutes apart) is indicated to reverse the effect of dabigatran when clinically indicated.^{1,5} Andexanet alfa (bolus and 2-hour infusion, with the dose dependent on the timing of exposure and the individual agent) is used to reverse the effect of the oral anti-Xa agents. Experience with these agents is accumulating.²⁻⁴ Prothrombin complex concentrate (or its activated form) has also been used with direct oral anticoagulant-related bleeding.
4. A systematic review of the effectiveness and safety of administering vitamin K to patients receiving VKA therapy with an INR between 4.5 and 10.0 and without bleeding indicated a nonsignificant increased risk of mortality and thromboembolism with vitamin K administration, with only moderate certainty of the evidence. Patients receiving vitamin K had a nonsignificant increase in the likelihood of reaching goal INR, with very low certainty of the evidence. The findings suggested that patients on VKA therapy who have an INR between 4.5 and 10.0 and are not bleeding are not likely to benefit from routine vitamin K administration in addition to temporary VKA cessation.¹³

11.5. Thromboembolic Events With Prosthetic Valves

Recommendations for Management of Thromboembolic Events With Prosthetic Valves		
COR	LOE	Recommendations
2a	C-EO	1. In patients with a mechanical AVR who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 2.5 (range, 2.0–3.0) to 3.0 (range, 2.5–3.5) or to add daily low-dose aspirin (75–100 mg), with assessment of bleeding risk.
2a	C-EO	2. In patients with a mechanical mitral valve replacement who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 3.0 (range, 2.5–3.5) to 4.0 (range, 3.5–4.0) or to add daily low-dose aspirin (75–100 mg), with assessment of bleeding risk.
2b	C-EO	3. In patients with a bioprosthetic surgical or transcatheter aortic valve or bioprosthetic mitral valve who experience a stroke or systemic embolic event while on antiplatelet therapy, VKA anticoagulation, instead of antiplatelet therapy may be considered after assessment of bleeding risk. ^{1,2}

Synopsis

For patients with a mechanical valve who suffer an embolic event, it is important to assess the adequacy

of VKA anticoagulation, document time spent in the therapeutic range, exclude IE, screen for new-onset AF, and consider whether an underlying hypercoagulable state might be a contributing factor. Thromboembolism in bioprosthetic heart valve recipients should similarly raise suspicion of IE or new-onset AF in the right clinical setting. Leaflet thrombosis occurs more frequently with bioprosthetic transcatheter aortic valves than with bioprosthetic surgical aortic valves.^{1–4} Intensification of antithrombotic therapy should always account for individual patient bleeding risk (Figure 13).

Recommendation-Specific Supportive Text

1. There are no comparative-effectiveness trials from which to assess the relative utility of higher-intensity VKA therapy versus standard VKA therapy plus low-dose aspirin in mechanical valve recipients who have experienced stroke or systemic embolism while in target INR range. Excluding the common clinical occurrence of extended time in a subtherapeutic INR range is the first priority. Assessment of medication adherence, intercurrent illness, new or recently adjusted medications, dietary changes, and alcohol intake is critical. Whether to intensify VKA therapy or add low-dose aspirin is a patient-specific, shared decision-making proposition that must weigh several factors, including bleeding risk.
2. The approach to management of the patient with a systemic embolic event and a mechanical mitral prosthesis includes review of INR levels to ensure the patient is in the target INR range most of the time. INR levels may have been subtherapeutic because of suboptimal medication adherence, intercurrent illness, new or recently adjusted medications, dietary changes, or alcohol intake. Whether to intensify VKA therapy or add low-dose aspirin is a patient-specific, shared decision-making proposition that must weigh several factors, including bleeding risk.
3. In those patients with a bioprosthetic valve who have a stroke or embolic event, further imaging with TEE or 3D CT scanning may show leaflet thrombosis, which should respond to anticoagulation with either a VKA or a NOAC.^{1,2} The effectiveness of anticoagulation in aortic and mitral bioprosthetic valve recipients in whom leaflet thrombosis cannot be established as the cause of thromboembolism is uncertain, and patients should undergo a full neurological evaluation to rule out other causes of the neurological event. Shared decision-making that accounts for bleeding risk is a central feature of management.

11.6. Acute Mechanical Valve Thrombosis

11.6.1. Diagnosis of Acute Mechanical Valve Thrombosis

Recommendation for Diagnosis of Acute Mechanical Valve Thrombosis

Referenced studies that support the recommendation are summarized in Online Data Supplement 38.

COR	LOE	Recommendation
1	B-NR	1. In patients with suspected mechanical prosthetic valve thrombosis, urgent evaluation with TTE, TEE, fluoroscopy, and/or multidetector CT imaging is indicated to assess valve function, leaflet motion, and the presence and extent of thrombus. ^{1–7}

Synopsis

Mechanical valve thrombosis is typically a subacute to acute event resulting in rapid valve dysfunction because of abnormal or absent motion of the valve leaflets, which often is associated with inadequate VKA anticoagulation. However, recurrent valve thrombosis can be associated with pannus ingrowth in the chronic setting. Mechanical valve thrombosis can present with rapid onset of symptoms or acute pulmonary edema. Physical examination may demonstrate a stenotic murmur and muffled closing clicks, and further urgent diagnostic evaluation is required. The annual rate of prosthetic valve thrombosis with mechanical valves ranges from 0.1% to 5.7%. Higher rates of mechanical valve thrombosis are seen for some specific valve types, within the first 3 months after valve implantation and, for mechanical valves implanted in the mitral or tricuspid position compared with the aortic position.⁸

Recommendation-Specific Supportive Text

1. Mechanical prosthetic valve thrombosis is diagnosed by an abnormally elevated velocity or gradient across the prosthesis, with either limited leaflet motion or attached mobile densities consistent with thrombus, or both. Prosthetic valve obstruction is usually defined as a mean transvalvular gradient increase >50% (or an increase >10 mm Hg across an aortic prosthesis) compared with baseline, after exclusion of other causes, such as a high-output state. When mechanical valve thrombosis is suspected, imaging and Doppler data from TTE provide information on valve function, estimated pulmonary pressures, and LV size and systolic function.⁹ Leaflet motion should be visualized with CT or TEE (particularly for a mitral prosthesis) or fluoroscopy (for an aortic prosthesis).^{6,7,10–12} Prolonged periods of observation under fluoroscopy or TEE may be required to diagnose intermittent obstruction. The presence and quantification of thrombus and pannus should be evaluated by either TEE or CT.^{6,7,10–12}

11.6.2. Intervention

Recommendation for Intervention for Mechanical Prosthetic Valve Thrombosis		
Referenced studies that support the recommendation are summarized in Online Data Supplement 38.		
COR	LOE	Recommendation
1	B-NR	1. For patients with a thrombosed left-sided mechanical prosthetic heart valve who present with symptoms of valve obstruction, urgent initial treatment with either slow-infusion, low-dose fibrinolytic therapy or emergency surgery is recommended. ¹⁻¹²

Synopsis

Patients presenting with a thrombosed mechanical valve require urgent therapy. The 2 options of low-dose, continuous-infusion thrombolytic therapy or emergency surgery are both effective, with the decision to proceed with either one based on multiple clinical factors and local experience and expertise.

Recommendation-Specific Supportive Text

1. The decision between surgery and systemic fibrinolysis for symptomatic left-sided mechanical valve thrombosis should be individualized (Table 23) after review by the heart valve team, while engaging the patient in a process of shared decision-making and accounting for local experience and expertise. The overall 30-day mortality rate with surgery is 10% to 15%, with a lower mortality rate of <5% in patients with NYHA class I or II symptoms.^{2,3,7} Recent studies using an echocardiogram-guided, slow-infusion, low-dose fibrinolytic protocol have shown hemodynamic success rates >90%, with embolic event rates <2% and major bleeding rates <2%.¹³ Systemic fibrinolysis is therefore an acceptable alternative to reoperation in patients at high or prohibitive surgical risk and in patients who have a small thrombus burden, mild HF symptoms (NYHA class I or II), and low bleeding risk. Absence of surgical expertise should be considered in the clinical decision-making process as a factor that favors thrombolytics, whereas recurrent valve thrombosis favors a surgical approach (Table 23).

11.7. Bioprosthetic Valve Thrombosis

11.7.1. Diagnosis of Bioprosthetic Valve Thrombosis

Recommendation for Diagnosis of Bioprosthetic Valve Thrombosis		
COR	LOE	Recommendation
2a	C-LD	1. In patients with suspected bioprosthetic valve thrombosis, 3D TEE or 4D CT imaging can be useful to rule out leaflet thrombosis. ¹⁻⁵

Synopsis

Bioprosthetic valve thrombosis is most common in the first 3 months after implantation but also has been described in patients years (typically 1 or 2) after valve implantation, with the longest interval being 6.5 years.⁶ Bioprosthetic valves are less thrombogenic than their mechanical counterparts. However, the diagnosis of subclinical bioprosthetic valve thrombosis has increased with use of CT imaging and as a function of the increased numbers of implanted bioprosthetic valves, including TAVI.¹⁻⁵

Recommendation-Specific Supportive Text

1. Bioprosthetic valve thrombosis appears to be more common with transcatheter than with surgical bioprosthetic valves. Leaflet thrombosis often is suspected on the basis of an increased transvalvular velocity on routine echocardiographic monitoring and can be confirmed by the finding of hypoattenuation of the valve leaflets on CMR imaging. When there is clinical evidence of stenosis, 3D TEE or 4D CT imaging may be useful to detect a layer of valve thrombus, which may respond to treatment with oral anticoagulation.

11.7.2. Medical Therapy

Recommendation for Medical Therapy		
Referenced studies that support the recommendation are summarized in Online Data Supplement 39.		
COR	LOE	Recommendation
2a	B-NR	1. In patients with suspected or confirmed bioprosthetic valve thrombosis who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable. ¹⁻⁶

Synopsis

Patients with an obstructed bioprosthesis may have a thin layer of thrombus causing reduced leaflet motion. VKA treatment may result in resolution of the thrombus and improvement in valve function.

Recommendation-Specific Supportive Text

1. Multiple small nonrandomized studies support the use of VKAs to treat patients with clinical and subclinical bioprosthetic valve thrombosis after both SAVR and TAVI.^{1,3,4,6,7} VKA anticoagulation can result in a significant reduction of transvalvular gradient, improved leaflet motion, and clinical improvement.^{4,6,8}

Table 23. Systemic Fibrinolysis Versus Surgery for Prosthetic Valve Thrombosis

Favor Surgery	Favor Fibrinolysis
Readily available surgical expertise	No surgical expertise available
Low surgical risk	High surgical risk
Contraindication to fibrinolysis	No contraindication to fibrinolysis
Recurrent valve thrombosis	First-time episode of valve thrombosis
NYHA class IV	NYHA class I, II, or III
Large clot (>0.8 cm ²)	Small clot (≤0.8 cm ²)
LA thrombus	No LA thrombus
Concomitant CAD in need of revascularization	No or mild CAD
Other valve disease	No other valve disease
Possible pannus	Thrombus visualized
Patient choice	Patient choice

CAD indicates coronary artery disease; and NYHA, New York Heart Association.

Adapted from several references.^{2,5,7,13,14}

11.8. Prosthetic Valve Stenosis

11.8.1. Diagnosis of Prosthetic Valve Stenosis

Recommendations for Diagnosis of Prosthetic Valve Stenosis Referenced studies that support the recommendations are summarized in Online Data Supplement 40.		
COR	LOE	Recommendations
1	B-NR	1. In patients with suspected mechanical or bioprosthetic valve stenosis, TTE and TEE are recommended to diagnosis the cause and severity of valve obstruction, assess ventricular function, and estimate pulmonary artery systolic pressure. ^{1,2}
1	C-EO	2. In patients with mechanical valve stenosis, fluoroscopy or cine-CT is recommended to assess motion of the mechanical valve leaflets.
2a	C-LD	3. In patients with bioprosthetic valve stenosis, 3D TEE or 4D CT imaging can be useful to rule out leaflet thrombosis. ³⁻⁷

Synopsis

Prosthetic valve stenosis can occur with both mechanical and bioprosthetic valves. Echocardiographic definitions of stenosis severity have been provided by the American Society of Echocardiography.¹ Obstruction of a mechanical valve may be caused by thrombus formation that leads to abnormal leaflet mobility, pannus ingrowth, or a combination of the two.⁸ Bioprosthetic valve stenosis may be caused by structural valve deterioration, with leaflet degeneration by thickening, calcification, or tear as the end stage of a slowly progressive process resulting in abnormal leaflet motion, or it may be attributable to other structural causes, including stent creep. Bioprosthetic valve stenosis may also be

attributable to nonstructural causes, such as endocarditis, leaflet thrombus, or pannus. The progressive stages are defined by the Valve Academic Research Consortium criteria.⁹

Recommendation-Specific Supportive Text

1. TTE and TEE assessment can appropriately detect and quantify prosthetic valve stenosis.¹ TTE within 3 months after valve implantation is useful to provide baseline data on valve hemodynamics and ventricular function. In some patients, the orifice area of the implanted prosthesis may be inadequate to meet the cardiac output demands of the patient, even when the prosthetic valve itself is functioning normally. This circumstance, termed patient–prosthesis mismatch, is associated with a high transvalvular gradient, persistent LV hypertrophy, and an increased rate of cardiac events after valve replacement.^{10,11} Diagnosis in the setting of bileaflet mechanical valves is complicated by nonlaminar patterns of blood flow, for which significant pressure recovery may be present; thus, a high velocity in the central narrow slit-like orifice may not correlate with prosthetic valve stenosis or patient–prosthesis mismatch. Prosthetic valve stenosis is distinguished from patient–prosthesis mismatch by comparison with the early postoperative baseline study and by visualization of the appearance and motion of the valve leaflets. Prosthetic valve stenosis is characterized by a clinical course of progressive increase in transvalvular velocity and pressure gradient in conjunction with abnormal thickened/calcified leaflets (for bioprosthetic valves) or evidence of pannus formation (with mechanical valves).
2. The motion of the leaflets of a mechanical valve is best evaluated radiographically with fluoroscopy or cine-CT imaging because strong reflections from the mechanical valve obscure motion on echocardiographic imaging in most patients, particularly as assessed on images from the trans-thoracic approach. With fluoroscopic imaging, the angle of imaging must be adjusted to demonstrate leaflet motion from a side view, permitting measurement of the angles of opening and closure that can be compared with expected values for that valve type. Cine-CT images are obtained at a high frame rate focused on the prosthetic valve in a 3D acquisition. Compared with fluoroscopy, cine-CT 3D images are less operator dependent for measuring opening and closing angles. In addition, cine-CT allows detection of pannus or thrombus on or adjacent

to the valve, which is not possible with fluoroscopy. When excessive gradients are present with normal leaflet motion and no thrombus, either patient–prosthesis mismatch or pannus formation is present (or both).

3. Stenosis of a bioprosthesis may occur because of progressive structural valve degeneration or pannus formation. However, stenosis can also occur because of a thin layer of thrombus on the valve cusps, which is reversible with oral anticoagulation therapy. Bioprosthetic valves are less thrombogenic than their mechanical counterparts. However, the diagnosis of subclinical bioprosthetic valve thrombosis has increased with the use of CT imaging and as a function of the increased numbers of implanted bioprosthetic valves, including TAVI.^{3–7} When there is clinical evidence of bioprosthetic valve stenosis, 3D TEE or 4D CT imaging may be useful to detect a layer of valve thrombus as the cause of the obstruction.

11.8.2. Intervention for Prosthetic Valve Stenosis

Recommendations for Intervention for Prosthetic Valve Stenosis Referenced studies that support the recommendations are summarized in Online Data Supplement 40.		
COR	LOE	Recommendations
1	B-NR	1. In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless surgical risk is high or prohibitive. ^{1–3}
2a	B-NR	2. For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center. ^{4,5}
2a	B-NR	3. For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable. ^{6–13}

Synopsis

Cumulative survival rates are higher with reoperative AVR than with transcatheter ViV treatment for prosthetic valve stenosis, and a surgical approach is associated with a reduced incidence of patient–prosthesis mismatch, reduced incidence of paravalvular leak, and lower aortic valve gradients.¹⁴ The VIVID (Valve-In-Valve International Data) registry examined outcomes with ViV treatment of 459 patients, of whom 40% had isolated stenosis and 30% had mixed lesions.⁴ Within 1 month after the ViV procedure, 7.6% of patients died and 1.7% had a major stroke. Of the survivors, 93% experienced good functional status (NYHA class I or II), with an overall 1-year survival rate of 83.2%.⁴ Some systematic reviews comparing outcomes of transcatheter ViV with those of repeat SAVR suggest that hemodynamic outcomes are similar, but stroke and bleeding risks are lower with ViV.¹⁵ There is a subset of

patients with bioprosthetic valve stenosis attributable to thrombus on the leaflets who may respond to oral anticoagulation with a VKA (Figure 14).^{6–13}

Recommendation-Specific Supportive Text

1. Reoperative surgery for prosthetic valve stenosis is associated with acceptable mortality and morbidity rates in the current era, but the risks are typically higher than those estimated at the time of initial surgery because of older patient age, clinical status at the time of intervention, and reoperative status.^{2,16} The decision to proceed with surgical versus transcatheter intervention is based on available expertise, individual patient and valve characteristics, and shared decision-making.
2. Catheter-based therapy with transcatheter ViV has emerged as an acceptable alternative to reoperative surgery for the treatment of high- and prohibitive-surgical risk patients with bioprosthetic AS.^{4,5} Although coronary artery obstruction is more common with aortic ViV procedures than with TAVI for native AS, rates of paravalvular leak and permanent pacemaker implantation are lower with aortic ViV procedures than with TAVI for native AS. Annulus rupture has not been reported. Transcatheter ViV also has been successfully performed for failed surgical bioprostheses in the mitral, pulmonic, and tricuspid positions, although LV outflow obstruction may occur after mitral ViV implantation.
3. A subset of patients presents with stenosis of a bioprosthetic valve attributable to leaflet thrombosis that results in decreased mobility of the leaflets. Leaflet thrombosis can occur from 1 month to years after implantation. If the patient is stable and has no contraindication to long-term anticoagulation, a trial of oral anticoagulation with VKA may result in resolution of the thrombus and improvement in hemodynamics.^{6–13} However, these patients are at increased risk of recurrent thrombosis (if the anticoagulation is stopped) and early structural deterioration, and thus they require close follow-up.¹⁷

11.9. Prosthetic Valve Regurgitation

Regurgitation in a mechanical prosthetic valve may be transvalvular, caused by impaired motion of the valve disk secondary to pannus, thrombus, or vegetation interfering with complete closure of the valve occluders, or paravalvular, caused by suture line disruption related to technical error at implantation, suture failure, annular disruption, or endocarditis. Patients with severe mitral annular calcification are particularly vulnerable to developing late paravalvular leak. Regurgitation in bioprosthetic valves may be paravalvular but more often is

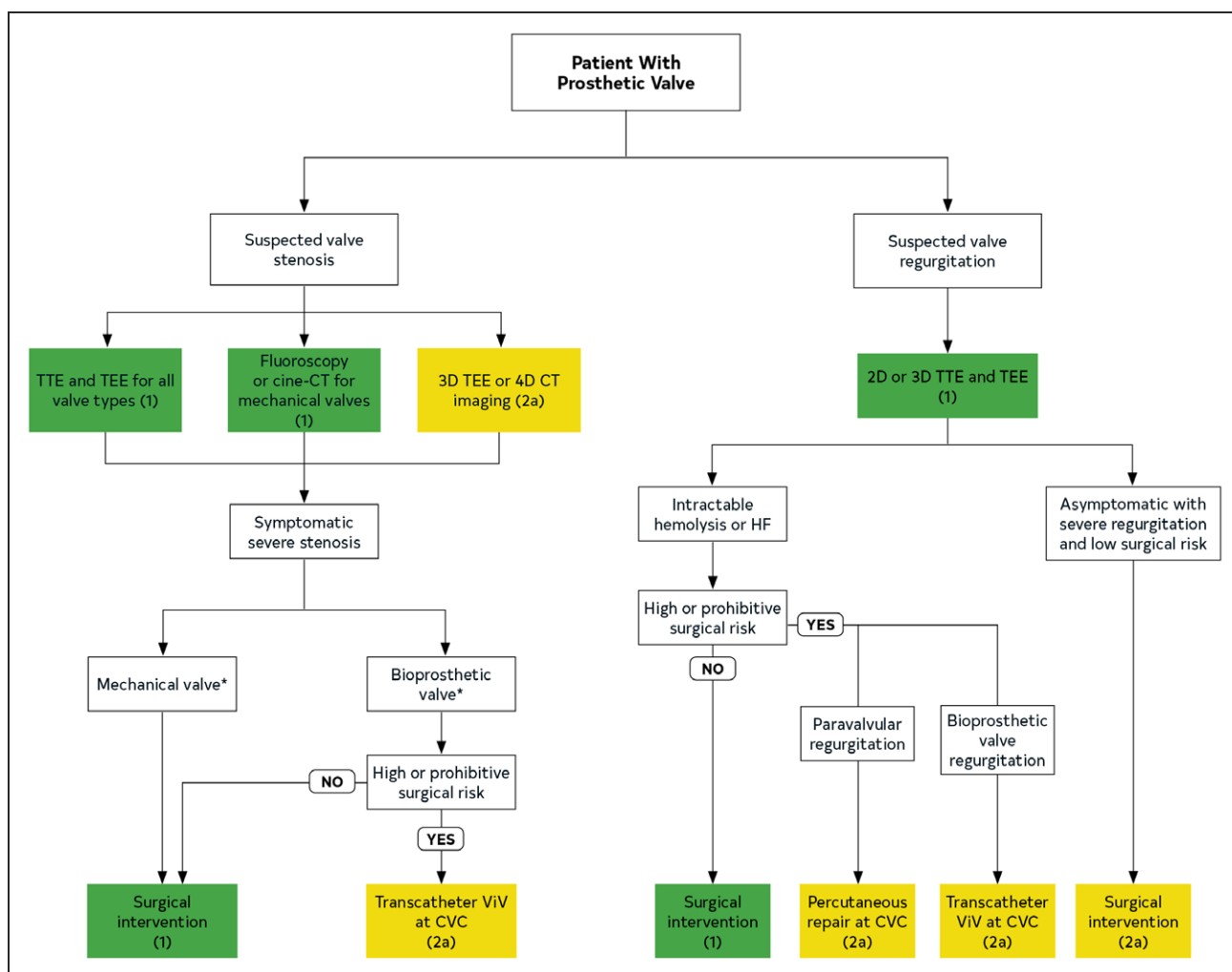


Figure 14. Management of prosthetic valve stenosis and regurgitation.

Colors correspond to Table 2. 3D indicates 3-dimensional; 4D, 4-dimensional; CT, computed tomography; CVC, Comprehensive Valve Center; HF, heart failure; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography/echocardiogram; and ViV, valve-in-valve.

*See Figure 13 if valve thrombosis is suspected.

transvalvular, caused by leaflet immobility secondary to calcification or leaflet perforation or flail associated with areas of focal calcification.¹ Echocardiographic definitions of prosthetic valve regurgitation severity have been published by the American Society of Echocardiography.²

11.9.1. Diagnosis of Prosthetic Valve Regurgitation

Recommendations for Diagnosis of Prosthetic Valve Regurgitation		
Referenced studies that support the recommendations are summarized in Online Data Supplement 41.		
COR	LOE	Recommendations
1	B-NR	1. In patients with suspected mechanical or bioprosthetic valve regurgitation, TTE and TEE are recommended to determine the cause and severity of the leak, assess ventricular function, and estimate pulmonary artery systolic pressure. ¹⁻⁴
1	C-EO	2. In patients undergoing a transcatheter procedure for paravalvular prosthetic regurgitation, 3D TEE is recommended for intraprocedural guidance. ⁴⁻⁷

Synopsis

The clinical presentation of prosthetic valve regurgitation varies depending on its severity, hemodynamic effects, and etiology. In asymptomatic patients, prosthetic valve regurgitation may be found incidentally on routine clinical or imaging follow-up. A change in auscultatory findings (eg, change in prosthetic valve sounds or a new murmur) should prompt suspicion of prosthetic valve dysfunction. Symptomatic patients with prosthetic valve regurgitation present with unexplained or new-onset HF or significant hemolysis with or without anemia. TTE is inadequate for evaluation of prosthetic mitral valves; TEE is needed when prosthetic MR is a concern. A critical step in evaluation of the patient with prosthetic valve regurgitation is to distinguish transvalvular from paravalvular leak, which also requires TEE in addition to TTE.

Recommendation-Specific Supportive Text

1. Echocardiography is the primary imaging modality to assess the location and quantify the severity of prosthetic valve regurgitation, often requiring both TTE and TEE approaches.^{1,3} Although TTE provides superior assessment of transvalvular gradients, chamber sizes, and function, TEE is better suited to identify the cause and location of regurgitation and is essential for prosthetic mitral valve because of acoustic shadowing on TTE. Even with prosthetic aortic valves, acoustic shadowing may affect detection of a paravalvular leak by either TTE or TEE, with TTE being suboptimal to assess posterior paravalvular leak and TEE suboptimal to assess anterior defects.³ The Valve Academic Research Consortium (VARC) has suggested an approach for assessment of paravalvular leak severity and constructed a 5-class grading scheme.⁷
2. 3D echocardiography plays a significant role in determining the precise location and size of the paravalvular leak in patients undergoing intervention. For a successful transcatheter paravalvular leak closure, adequate paravalvular leak assessment includes 1) precise location of the defect(s), 2) precise dimensions, 3) orientation of the defect in relation to the sewing ring and prosthetic valve occluders or leaflets, and 4) location and orientation of the subvalvular structures. Real-time 3D TEE allows optimal visualization of the defects and direct guidance for catheter movement and positioning of the implanted device(s) during the transcatheter closure procedure.^{4,5} 3D TEE also allows assessment of residual regurgitation after device placement. Limitations of 3D TEE include artifacts of ultrasound imaging (eg, dropout, acoustic shadowing, reverberation artifacts) and reduced temporal and spatial resolution.⁸ Transcatheter closure using intracardiac echocardiography guidance is possible and alleviates the need for conscious sedation or anesthesia but allows only 2D and color Doppler imaging.⁹

11.9.2. Medical Therapy

Medical therapy for prosthetic valve regurgitation is appropriate in asymptomatic patients or when the cause of regurgitation is valve thrombosis (see Sections 11.6 and 11.8) or prosthetic valve endocarditis (see Section 12.3), although further intervention may ultimately be needed in many of these patients. Some patients tolerate asymptomatic prosthetic valve regurgitation for many years, similar to patients with native valve regurgitation. However, there may be patients who develop rapid progression of the severity of bioprosthetic valve regurgitation because of leaflet degeneration. In patients with hemolytic anemia attributable to paravalvular regurgitation, medical management with folic acid and iron supplementation or periodic transfusion may be possible when the anemia is

not severe, with intervention reserved for patients with symptomatic intractable anemia (see Section 11.8.3).

11.9.3. Intervention

Recommendations for Intervention		
Referenced studies that support the recommendations are summarized in Online Data Supplement 41.		
COR	LOE	Recommendations
1	B-NR	1. In patients with intractable hemolysis or HF attributable to prosthetic transvalvular or paravalvular leak, surgery is recommended unless surgical risk is high or prohibitive. ¹⁻⁴
2a	B-NR	2. In asymptomatic patients with severe prosthetic regurgitation and low operative risk, surgery is reasonable. ¹⁻⁴
2a	B-NR	3. In patients with prosthetic paravalvular regurgitation with the following: 1) either intractable hemolysis or NYHA class III or IV symptoms and 2) who are at high or prohibitive surgical risk and 3) have anatomic features suitable for catheter-based therapy, percutaneous repair of paravalvular leak is reasonable when performed at a Comprehensive Valve Center. ⁵⁻⁹
2a	B-NR	4. For patients with severe HF symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center. ¹⁰⁻¹²

Synopsis

Prosthetic valve degeneration can result in regurgitation attributable to leaflet calcification and noncoaptation or leaflet degeneration with a tear or perforation. Acute or chronic severe regurgitation may result in HF symptoms and signs. Paravalvular leak may result in hemolysis with symptoms attributable to anemia and HF. New paravalvular leak late after valve implantation raises the concern for IE, which should be excluded because the presence of infection would require antibiotic treatment before surgical therapy and would be a contraindication to transcatheter therapy. Symptomatic patients with paravalvular leak around a prosthetic valve are best managed by surgery, with percutaneous closure of the leak if the patient is at high or prohibitive surgical risk. Symptomatic patients with bioprosthetic valve regurgitation are best managed by surgery, with a transcatheter ViV procedure if the patient is at high or prohibitive risk. Because of rapid progression of bioprosthetic regurgitation, replacement of a leaking bioprosthesis may be considered even in the asymptomatic patient.

Recommendation-Specific Supportive Text

1. Surgery is a viable therapeutic option in many patients with symptomatic paravalvular leak and is associated with reasonable outcomes.¹ The risks associated with surgical intervention depend on the procedure required, be it suture repair or

repeat AVR. Although surgical reoperation is associated with acceptable mortality and morbidity rates in the current era, it still carries a higher risk than the initial surgery. Kaneko and colleagues examined a cohort of 3380 patients from the STS database (2011–2013) who underwent elective isolated reoperative AVR, and they demonstrated a higher (but acceptable) operative mortality rate than that seen with initial AVR (4.6% versus 2.2%; $P<0.0001$) and relatively low complication rates.¹³ This was true even among octogenarians who underwent reoperative AVR.³ In a cohort of 136 consecutive patients who underwent surgical correction for a non–endocarditis-related aortic or mitral paravalvular leak (1986–2001), surgical correction of the paravalvular leak was associated with acceptable operative mortality (6.6%) and morbidity rates.¹ More recently, Shah and colleagues reported an operative mortality rate of 3% among 495 patients undergoing surgery for paravalvular leak,¹⁴ with higher risk associated with mitral than with aortic valve procedures (odds ratio: 1.66; 95% CI: 1.25–2.20). These findings are consistent with the findings of Bouhout and colleagues,¹⁵ who reported operative mortality rates of 8% among mitral valve, 3% among aortic valve, and 14% among double-valve patients in a total cohort of 190 patients undergoing surgery indicated for paravalvular leak. Estimates of operative risk for individual patients can be calculated by using the STS risk calculator (<http://riskcalc.sts.org/stswebriskcalc/>).¹⁶

2. Prosthetic valve deterioration can result in regurgitation attributable to leaflet calcification and non-coaptation or leaflet degeneration with a tear or perforation. Even in asymptomatic patients with severe prosthetic regurgitation, valve replacement is reasonable because of the risk of sudden clinical deterioration if further leaflet tearing occurs. IE should be excluded or concurrently treated. If a “watchful waiting” approach is taken in asymptomatic patients with severe prosthetic valve regurgitation, referral to a Comprehensive Heart Valve Center is prudent.
3. In some patients, operative risk is high, or surgery is not feasible. Nonrandomized studies have demonstrated clinical success with percutaneous paravalvular leak closure performed by expert operators under the supervision of an MDT at a Comprehensive Valve Center. Procedural success rates for percutaneous paravalvular leak closure, typically defined by no more than mild residual regurgitation and the absence of death and major complications, are highly variable. In a large single-center cohort, percutaneous repair of 141 paravalvular defects was attempted in 115 patients, with an achieved overall

success rate of 77% and a 30-day complication rate of 8.7%.⁶ In another study of 126 patients who underwent percutaneous paravalvular leak repair, Sorajja and colleagues reported a 3-year survival rate of 64.3%.⁵ The degree of residual regurgitation affects symptom improvement and survival. In a cohort of 231 consecutive patients (2006–2017) who underwent percutaneous mitral paravalvular leak closure, the reduction of paravalvular leak to mild or less was achieved in 70% of patients.^{7,8} Those patients with mild or less residual paravalvular leak had a survival rate at 3 years of 61%, compared with a rate of 47% in patients with greater degrees of residual paravalvular leak ($P=0.002$).^{7,8} Notably, treatment of HF symptoms with paravalvular leak closure is more successful than is treatment of hemolysis. IE should be excluded before attempted paravalvular leak repair.

4. The Valve-In-Valve International Data registry examined outcomes of transcatheter ViV procedures in 459 patients, of whom about 30% had isolated regurgitation and 30% had mixed lesions.¹⁰ Within 1 month after the ViV procedure, 7.6% of patients died, 1.7% had a major stroke, and 93% of survivors experienced good functional status. The 1-year survival rate was 83.2%.¹⁰ Several systematic reviews have compared outcomes of transcatheter ViV with those of reoperative SAVR. In 1 report, ViV had similar hemodynamic outcomes to repeat surgery and lower stroke risk and bleeding risk than repeat surgery.¹¹ A meta-analysis of 498 patients demonstrated no significant differences in early and mid-term all-cause mortality rates with ViV or reoperation.¹⁷ In another meta-analysis of 342 patients, reoperative AVR was compared with transcatheter ViV for failed degenerated aortic bioprosthesis and the group undergoing reoperative AVR had a lower all-cause mortality with superior hemodynamic outcomes.¹⁸ Thus, although transcatheter ViV appears to be a safe and feasible alternative to repeat SAVR in patients who are inoperable or at high surgical risk, repeat SAVR should remain the standard of care, particularly in low-risk patients.¹⁸

12. INFECTIVE ENDOCARDITIS

12.1. Classification of Endocarditis

Endocarditis is classified according to whether a native or prosthetic valve is affected and by timing of infection after valve intervention. Prevention of endocarditis is important in all patients with valve disease, both before and after valve replacement or intervention (see Section 2.4.2). The risk factors involved with IE and the predominating causative organisms have evolved over

time, with a recent increased incidence of drug use–associated IE. IE is fatal unless treated appropriately, and there are no asymptomatic patients with endocarditis. The in-hospital mortality rate for IE is 15% to 20%, with a 1-year mortality rate approaching 40%. Noninfective types of endocarditis are not addressed in these guidelines.

12.2. Diagnosis of IE

Recommendations for Diagnosis of IE		
Referenced studies that support the recommendations are summarized in Online Data Supplement 42.		
COR	LOE	Recommendations
1	B-NR	1. In patients at risk of IE (eg, those with congenital or acquired VHD, previous IE, prosthetic heart valves, certain congenital or heritable heart malformations, immunodeficiency states, or injection drug use) who have unexplained fever blood, culture samples should be obtained. ¹
1	B-NR	2. In patients with the recent onset of left-sided valve regurgitation, at least 2 sets of blood culture samples should be obtained. ^{1–12}
1	B-NR	3. In patients with suspected IE, the Modified Duke Criteria should be used for diagnosis (Tables 24 and 25). ^{2–10}
1	B-NR	4. Patients with IE should be evaluated and managed with consultation with a multispecialty Heart Valve Team, which includes an infectious disease specialist, cardiologist, and cardiac surgeon; a cardiac anesthesiologist for surgically managed patients ¹¹ ; and a neurologist for patients with neurological events. ^{11–13}
1	B-NR	5. In patients with suspected IE, TTE is recommended to identify vegetations, characterize the hemodynamic severity of valvular lesions, assess ventricular function and pulmonary pressures, and detect complications. ^{14–23}
1	B-NR	6. In all patients with known or suspected IE and nondiagnostic TTE results, when complications have developed or are clinically suspected or when intracardiac device leads are present, TEE is recommended. ^{21,23–40}
1	B-NR	7. In patients with IE who have a change in clinical signs or symptoms (eg, new murmur, embolism, persistent fever, HF, abscess, or atrioventricular heart block) and in patients at high risk of complications (eg, extensive infected tissue, large vegetation on initial echocardiogram, or staphylococcal, enterococcal, or fungal infections), TTE and/or TEE are recommended for reevaluation. ^{24,31,41–46}
1	B-NR	8. In patients undergoing valve surgery for IE, intraoperative TEE is recommended. ^{47–50}
1	B-NR	9. In patients being considered for an early change to oral antibiotic therapy for the treatment of stable IE, a baseline TEE before switching to oral therapy and a repeat TEE 1 to 3 days before completion of the oral antibiotic regimen should be performed. ⁵¹

Recommendations for Diagnosis of IE (Continued)		
COR	LOE	Recommendations
2a	B-NR	10. In patients with <i>Staphylococcus aureus</i> bacteremia without a known source, TEE is reasonable to diagnose possible IE. ^{11,36,52–56}
2a	B-NR	11. In patients with a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur, a TEE is reasonable to aid in the diagnosis of IE. ^{57–60}
2a	B-NR	12. In patients in whom the anatomy cannot be clearly delineated by echocardiography in the setting of suspected paravalvular infections, CT imaging is reasonable. ^{37,61–68}
2a	B-NR	13. In patients classified by Modified Duke Criteria as having “possible IE,” ¹⁸ F-fluorodeoxyglucose PET/CT is reasonable as adjunct diagnostic imaging. ^{69–71}
2b	B-NR	14. In patients with nosocomial <i>S. aureus</i> bacteremia with a known portal of entry from an extracardiac source, TEE might be considered to detect concomitant staphylococcal IE. ^{22,53,54,72–74}

Synopsis

In patients with suspected endocarditis, the Modified Duke Criteria (Tables 24 and 25) are the current standard for diagnosis and incorporate clinical, imaging, and bacteriological criteria. These criteria have been well validated by comparison with surgical or autopsy findings and in the clinical outcomes of numerous studies involving a wide spectrum of patients, including children, the elderly, prosthetic valve recipients, injection drug users, and non-drug users, as well as patients in both primary- and tertiary-care settings. For patients with VHD and known or suspected IE, obtain blood culture results before initiation of antibiotic therapy. For diagnosis and management of patients with IE, additional members of the Heart Valve MDT include infectious disease experts, who can provide advanced approaches to microbiological diagnosis. Cardiac imaging with TTE, TEE, and now CT and CT/PET imaging is critical for diagnosis of IE.^{4,6–10}

Recommendation-Specific Supportive Text

1. Blood culture results are positive in 90% of patients with IE provided that ≥ 2 blood culture samples are obtained at different times, ideally >6 hours apart if clinical status allows, at peripheral sites before initiation of antimicrobial therapy. More important than the time interval of the collection of culture samples is observing strict aseptic technique, avoiding sampling from intravascular lines, and ensuring an adequate volume of blood for the culture sample. Routine incubation of blood culture samples for >7 days is no longer necessary in the era of continuous-monitoring blood culture

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

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

IE indicates infective endocarditis.

Adapted from Durack DT, et al,² and Li JS, et al.⁴

systems and non-culture-based technology. In the 10% of patients with culture-negative endocarditis, serological testing or advanced laboratory diagnostics (eg, polymerase chain reaction) may be helpful to identify the etiologic agent.^{1,42,75–78}

- The recent onset of new or increased left-sided valve regurgitation, detected by the presence of a new or louder murmur followed by TTE confirmation, may be attributable to endocarditis, so it is prudent to obtain blood culture samples to exclude this diagnosis.
- The Modified Duke Criteria (Tables 24 and 25) have been well validated by comparison with surgical or autopsy findings and in the clinical outcomes of numerous studies involving a wide spectrum of patients, including children, the elderly, prosthetic valve recipients, injection drug users, and non-drug users, as well as patients in both primary- and tertiary-care settings. About three-fourths of patients with IE are diagnosed within 30 days of the onset of infection, so classic clinical features of IE, such as embolic or vasculitic skin lesions, renal disease caused by immune complex deposition, and immunologic abnormalities, are often absent. In these cases, maintaining a high level of clinical suspicion with regard to the possibility of IE in patients who are susceptible is paramount.^{4,6–10}

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

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

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

IE indicates infective endocarditis; IgG, immunoglobulin G; and spp, species.

Adapted from Durack DT, et al,² and Kupferwasser LI, et al.³

- The diagnosis of IE can still be difficult and is frequently delayed, which may cause progressive and potentially irreparable structural damage to the heart and other organ systems secondary to vascular-embolic and immunologically mediated events. Additionally, stroke (16.9%), embolization other than stroke (22.6%), HF (32.3%), intracardiac abscess (14.4%), and the need for surgical therapy (48.2%) remain common. Patients with suspected IE are most optimally managed in an environment that coordinates the management of specialists who are well attuned to the various organ systems, pathological processes, and potential treatment

modalities involved, ideally at centers with immediate access to cardiac surgery during the initial observation stages of the disease. With the emerging use of telemedicine, it may be reasonable to manage patients with lower-acuity IE in a center without on-site multispecialty care by telecommunication with a Heart Valve MDT and infectious disease specialists, with rapid transfer of the patient to a Comprehensive Valve Center if needed.^{11–13}

5. The presence of valvular vegetation is a major criterion in the diagnosis of IE. TTE has a sensitivity between 50% and 90% and a specificity >90% for detection of vegetations in native valve endocarditis. TTE has a sensitivity of only 36% to 69% in prosthetic valve endocarditis, but TTE still has a role in these patients for detection and quantitation of valve dysfunction (even in the challenging situation of regurgitation in the mechanical prosthetic mitral valve, for which a proximal convergence zone may provide important evidence for a paravalvular leak), evaluation of ventricular size and systolic function, and estimation of pulmonary pressures. TTE exhibits superior imaging over TEE for the anterior aspect of a prosthetic aortic valve, which is commonly shadowed by the valve on TEE. TTE also allows measurement of aortic transvalvular velocity/gradient, which is not always possible on TEE. Although TTE will not definitively exclude vegetations or abscesses in IE, it can identify very high-risk patients, establish the diagnosis, and guide early treatment decisions (Figure 8).^{14,19–23}
6. The sensitivity of TEE in native valve endocarditis ranges from 90% to 100%, with sensitivity ranges slightly lower in prosthetic valve endocarditis. TEE is superior to TTE in the visualization of both vegetations and paravalvular complications, which can be anatomic (eg, valve perforation, abscesses, and pericardial effusion) or hemodynamic (eg, valve regurgitation, fistulae, and intracardiac thrombi) in nature. TTE and TEE are complementary for the comprehensive evaluation of hemodynamics and anatomy in patients with IE. TEE should be used as an adjunct in patients with echocardiographic features of IE on TTE to rule out the presence of findings such as abscesses, which may alter the therapeutic approach to the management of the patient. TEE also serves a vital role in reassessment of patients with known IE with suspected clinical complications, as well as a guiding tool in the intraoperative assessment and management of the patient with IE. The timing of repeat examinations depends on the clinical presentation and course and on the virulence of the microorganism. Increasing vegetation

size under therapy must be considered a risk factor for new embolic events, whereas unchanged or reduced vegetation size under therapy may be more difficult to interpret.^{23,29,32–40}

7. HF, paravalvular extension, and embolic events represent the 3 most frequent and severe complications of IE. They are also the 3 main indications for early surgery, which is performed in almost 50% of cases. If signs or symptoms consistent with any of these complications exist, there should be a very low threshold for repeat imaging in these patients. TEE may miss initial paravalvular abscesses, particularly when the study is performed early in the patient's illness. In such cases, the incipient abscess may be seen only as nonspecific paravalvular thickening, which on repeat imaging across several days may become recognizable as it expands and cavitates. Similarly, paravalvular fistulae and pseudoaneurysms develop over time, and negative early TEE images do not exclude the potential for their development. A single negative TEE study cannot rule out underlying IE, and a repeat TEE study should be performed when a suspicion of persistence of infection remains or if complications ensue. Conversely, in the absence of clinical deterioration or new signs and symptoms, routine follow-up echocardiography is probably of only limited clinical utility.^{24,41,42,44–46}
8. Intraoperative TEE during cardiac surgery has an important role in the evaluation and quality control of a large variety of pathologies. Clinical and echocardiographic characteristics may change during an episode of IE because of the prolonged active phase and fluctuating course of this disease. Even if preoperative TEE has been performed, vegetation change/embolization or extension of the infectious process beyond the valve tissue may occur. In addition, other valves may become involved as the disease timeline progresses. Intraoperative TEE has been invaluable for baseline reassessment of anatomic or hemodynamic changes that may occur in the interval between the diagnostic echocardiogram and the time of surgery. TEE is also an important monitoring tool for evaluation of operative complications, such as air emboli, and an important adjunct to ensure the quality of the intended surgical result.^{49,50}
9. The recently published randomized POET (Partial Oral Treatment of Endocarditis) trial studied 400 patients with "stable" left-sided IE caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci. Patients who had been on intravenous antibiotics for at

least 10 days were randomized to continuation of the usual course of intravenous antibiotics or discharge to ambulatory treatment with oral antibiotics. As part of the study protocol, patients were reassessed by TEE within 1 to 3 days of completion of their assigned treatment to confirm that the patient had a sufficient response to therapy. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen. At 6 months after antibiotic treatment completion, the switch to early oral antibiotic therapy was noninferior to traditional long-term intravenous therapy.⁵¹

10. IE in patients with *S. aureus* bacteremia frequently involves normal cardiac valves and is seldom accompanied by the physical stigmata of IE, rendering the diagnosis of the disease difficult. Reliance on physical examination findings and clinical stigmata is likely to result in underdiagnosis of *S. aureus* IE in a large number of cases. TEE is cost-effective to guide duration of therapy in patients with intravascular catheter-associated *S. aureus* bacteremia, patients with intracardiac electronic devices, or other patients at higher risk of IE (including those with previous prosthetic valve surgery) or associated complications. Despite early diagnosis and appropriate therapy, IE after *S. aureus* bacteremia is frequently associated with disabling and life-threatening sequelae. The overall mortality rate of *S. aureus* IE ranges from 19% to 65%. Other complications include HF (20%–50%), paravalvular cardiac abscesses (30%–40%), neurological manifestations (30%), and systemic embolization (40%).^{11,36,55,56}
11. When compared with native valve endocarditis, prosthetic valve endocarditis is characterized by a lower incidence of vegetations (especially in mechanical prostheses) and a higher incidence of annular abscess and other paravalvular complications. Because cardiac auscultation may also be less revealing in prosthetic valve endocarditis and because ordinarily less virulent organisms may cause more anatomic destruction before culture or serological detection, early use of TEE in these high-risk patients is important. The sensitivity of TEE for detecting IE is lower with prosthetic valves than with native valves, so the importance of comparing serial echocardiographic studies is paramount to making the diagnosis.^{59,60}
12. Electrocardiographic-synchronized, multidetector-row CT is emerging as an important tool for non-invasive cardiac assessment and may be helpful in evaluating complications of IE. CT may also be

indicated in right-sided IE to demonstrate the presence of septic pulmonary infarcts and abscesses. Although CT is less accurate than TTE and TEE for identifying valvular vegetation and valvular perforations, CT is useful for evaluating patients with equivocal findings on TEE and for evaluating complications in patients with suspected paravalvular infection. CT imaging is particularly useful in pre-operative evaluation of patients with aortic valve IE to evaluate coronary artery and aortic involvement. In suspected prosthetic valve endocarditis, cardiac CT is less affected by the shadowing of mechanical valves or bioprosthetic valve sewing rings than is ultrasonography. CT also allows evaluation of the motion of mechanical valve occluders and provides visualization of thrombus or infective material limiting valve occluder motion. Additional imaging modalities, such as cardiac valvular fluoroscopy, can be an adjunct to other clinical and imaging information to detect the presence of obstructive disease in mechanical prosthetic valves affected by IE.^{61,64–68}

13. Diagnosis of IE can still be a vexing undertaking. It has been shown that the use of ¹⁸F-fluorodeoxyglucose PET/CT at the initial presentation of patients with suspected prosthetic valve endocarditis increases the diagnostic capability of the Modified Duke Criteria. The inclusion of abnormal ¹⁸F-fluorodeoxyglucose cardiac uptake as a major criterion addition to the Modified Duke Criteria enabled a recategorization of 76% of patients with prosthetic valve endocarditis initially classified as “possible” IE on admission to the hospital to “definite” IE. This tool must be used in centers with great experience with the technology, as this imaging technique may also be prone to false-positive results because of sterile inflammation in implanted prosthetic valves. ¹⁸F-fluorodeoxyglucose PET/CT may also be considered a complementary diagnostic tool for some patients with suspected native valve endocarditis.^{69–71}
14. Because the frequency of IE among patients with *S. aureus* bacteremia is reported to be approximately 30%, with many cases not being clinically suspected, TEE may be considered in the setting of *S. aureus* bacteremia to rule out IE. Even in *S. aureus* bacteremia from a known extracardiac source, such as an infected joint or joint prosthesis, TEE might be considered, given known cases of seeding of valve tissue in this type of setting. Possible exceptions are patients who have no underlying cardiac predisposing conditions or clinical signs of IE whose fever and bacteremia resolve within 72 hours after removal of a likely

infected focus (such as intravascular catheter removal). In the absence of 1) prolonged bacteremia lasting >4 days, 2) a permanent intracardiac device, 3) hemodialysis dependency, or 4) spinal infection or nonvertebral osteomyelitis, the risk of IE is relatively low, and routine TEE may not be necessary.^{22,53,54,74}

12.3. Medical Therapy

Recommendations for Medical Therapy for IE Referenced studies that support the recommendations are summarized in Online Data Supplement 42.		
COR	LOE	Recommendations
1	B-NR	1. In patients with IE, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the MDT. ¹⁻⁷
1	B-R	2. Patients with suspected or confirmed IE associated with drug use should be referred to addiction treatment for opioid substitution therapy. ⁸⁻¹⁰
2a	B-NR	3. In patients with IE and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. ¹¹⁻²⁴
2b	B-R	4. In patients with left-sided IE caused by streptococcus, <i>Enterococcus faecalis</i> , <i>S. aureus</i> , or coagulase-negative staphylococci deemed stable by the MDT after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if TEE before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up TEE can be performed 1 to 3 days before the completion of the antibiotic course. ²⁵
2b	B-NR	5. In patients receiving VKA anticoagulation at the time of IE diagnosis, temporary discontinuation of VKA anticoagulation may be considered. ^{13,26-34}
3: Harm	C-LD	6. Patients with known VHD should not receive antibiotics before blood cultures are obtained for unexplained fever. ^{22,35,36}

Synopsis

Details of specific antimicrobial regimens have been published previously by the AHA, European Society of Cardiology, and British Society for Antimicrobial Chemotherapy and are not repeated in this guideline. In patients on anticoagulant therapy for AF or a mechanical heart valve, continued anticoagulation is associated with a higher risk of intracranial bleeding, particularly after an embolic event. In patients with suspected intravenous drug use, effective long-term therapy includes referral to an addiction treatment program. In a select subset of patients with a stable clinical course, it may be possible to convert from intravenous to oral

antibiotics if TEE confirms the absence of paravalvular extension of the infection. In addition to antibiotic therapy, early surgical intervention often (approximately 50% of the time) is needed to manage infection and the sequelae of valve leaflet and paravalvular tissue destruction (Figure 15).^{1,2,37-42}

Recommendation-Specific Supportive Text

- Optimal treatment of IE is based on the appropriately timed initiation of antimicrobial therapy that is effective against the specific infective organism involved. Empirical therapy may be necessary in patients with septic shock or patients who show high-risk signs on presentation. Although no RCTs have been performed with regard to the use of antibiotic therapy in IE, the mortality rate before the antibiotic age neared 100%. Specific antimicrobial regimens, depending on the causative microorganism, have been published by the British Society for Antimicrobial Chemotherapy and the AHA. Because there are continuous changes in antimicrobial sensitivity over time, as well as regional and site-specific differences in antimicrobial susceptibility profiles, concomitant management with the assistance of a consultant thoroughly familiar with these patterns is imperative.¹⁻⁷
- Drug use–associated endocarditis is associated with a significantly higher complexity of care, with increased rates of readmission, reinfection, and recurrent need for repeat interventions, and its incidence has risen 12-fold over the past decade. Addiction specialists are an important part of the Heart Valve Team for this patient population. Addiction studies have shown that treatment outcomes for behavioral interventions alone for opioid use disorders are dismal, with >80% of patients returning to drug use. Some data show that patients who used pharmacotherapy, such as agonist therapy (opioid substitution therapy), in addition to behavioral treatments had a 50% reduction in relapse compared with those who used behavioral therapies alone.⁸⁻¹⁰
- Stroke in patients with IE can have several mechanisms, including hemorrhagic transformation of an ischemic infarct, septic erosion of an atherosclerotic vessel without aneurysm formation, and rupture of a mycotic aneurysm. Up to 35% of all patients with IE develop clinically evident systemic emboli. If more sensitive tests, such as magnetic resonance imaging, are used, a much higher proportion of patients with IE have evidence of emboli. In these patients, the most common cause of stroke is septic embolus

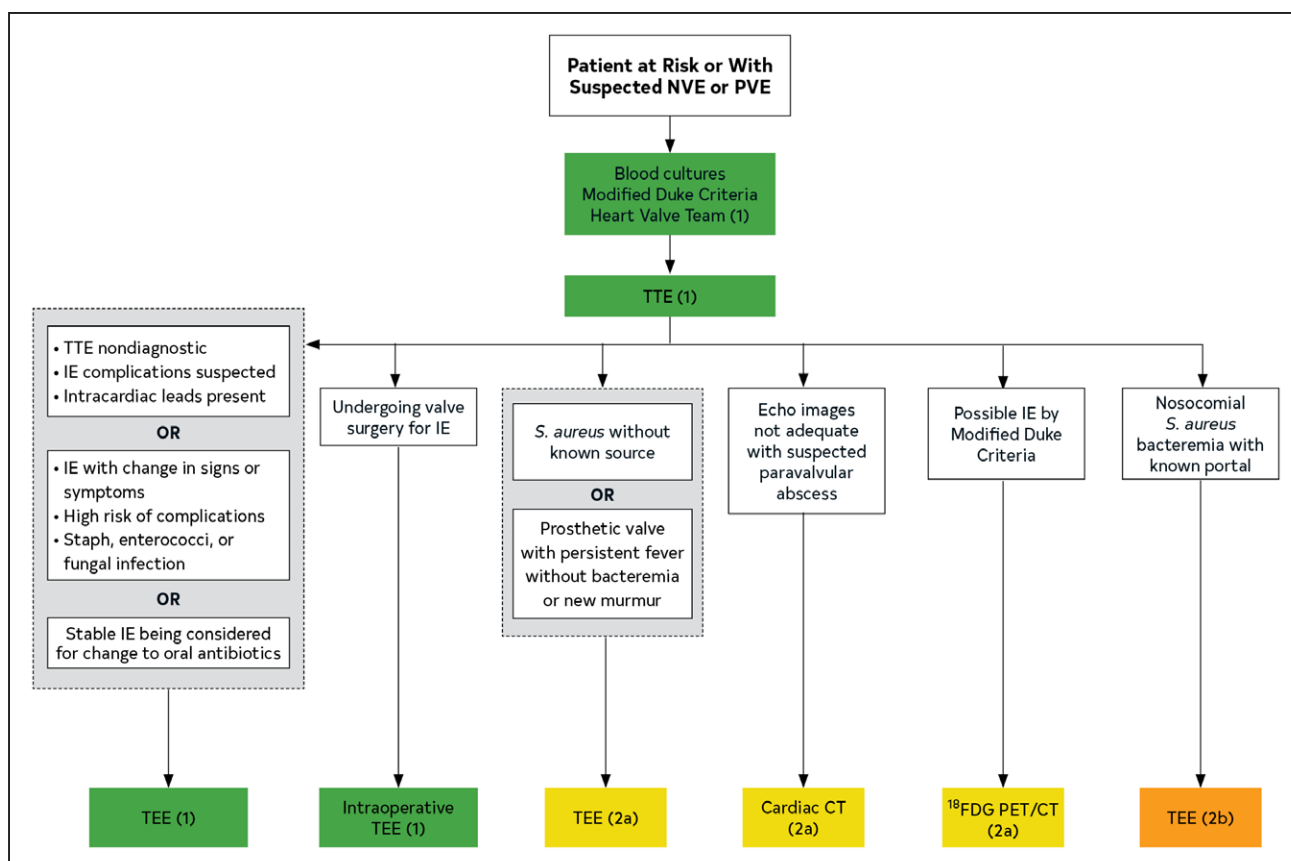


Figure 15. Diagnosis of IE.

Colors correspond to Table 2. CT indicates computed tomography; IE, infective endocarditis; ¹⁸FDG, ¹⁸F-fluorodeoxyglucose; NVE, native valve endocarditis; PET, positron emission tomography; PVE, prosthetic valve endocarditis; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

resulting in ischemia, often followed by hemorrhagic transformation. Anticoagulant therapy may increase the risk of an embolic infarct converting to a hemorrhagic infarct, and this risk must be weighed against the higher risk of recurrent embolization and valve dysfunction, particularly in patients on anticoagulation for a prosthetic valve. A specialist in the field of neurology or neuroradiology should be added to the Heart Valve Team when stroke complicates IE.^{11,18–24}

4. POET randomized stable patients who had left-sided endocarditis caused by streptococcus, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococci to treatment arms of continued intravenous treatment or a switch to oral antibiotic treatment after antibiotics had been administered intravenously for at least 10 days. Within 1 to 3 days before the completion of the assigned antibiotic treatment, TEE was performed to confirm that the patient had a sufficient response to treatment as part of this protocol.²⁵

5. In patients with native valve endocarditis, routine use of VKA is not recommended. In patients on VKA for other indications who have IE, VKA discontinuation should be considered at the initial presentation for several reasons: 1) the risk of bleeding associated with any needed urgent invasive procedures, 2) the risk of hemorrhagic stroke, and 3) the possible need for early surgery, which is required in roughly 50% of patients with prosthetic valve endocarditis. There are no RCTs studying the use of bridging therapy with intravenous or subcutaneous anticoagulant therapy in patients with IE, but observational studies suggest an increased risk of hemorrhagic stroke in patients on intravenous UFH during the acute phase of acute IE. Decisions about continued anticoagulation and antiplatelet therapy should ultimately be directed by the patient's cardiologist and cardiothoracic surgeon, in consultation with a neurology specialist if neurological findings are clinically present or noted on imaging.^{11,27–34}
6. Two sets of blood culture samples are the minimum for a secure microbiological diagnosis of IE.

Antibiotic therapy is most effective if the identity and sensitivities of the responsible organism are known. *S. aureus* is the most common pathogen responsible for prosthetic valve endocarditis but still accounts for only 23% of cases. The leading cause of "culture-negative IE" is the use of antibiotics before blood cultures are obtained. Negative blood cultures in the setting of IE delay diagnosis and often require additional serological and polymerase chain reaction testing.^{22,35,36}

12.4. Intervention

Recommendations for Intervention for IE Referenced studies that support the recommendations are summarized in Online Data Supplement 42.		
COR	LOE	Recommendations
1	B-NR	1. Decisions about the timing of surgical intervention for IE should be made by a Heart Valve Team. ¹⁻⁶
1	B-NR	2. In patients with IE who present with valve dysfunction resulting in symptoms of HF, early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) is indicated. ⁷⁻¹⁹
1	B-NR	3. In patients with left-sided IE caused by <i>S. aureus</i> , a fungal organism, or other highly resistant organisms, early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) is indicated. ^{7,9,15,20-35}
1	B-NR	4. In patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions, early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) is indicated. ^{7,9,36-44}
1	B-NR	5. In patients with IE and evidence of persistent infection as manifested by persistent bacteremia or fevers lasting >5 days after onset of appropriate antimicrobial therapy, early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) for IE is indicated. ^{7,9,15,25,26,45-48}
1	B-NR	6. In all patients with definite endocarditis and an implanted cardiac electronic device, complete removal of the pacemaker or defibrillator systems, including all leads and the generator, is indicated. ⁴⁹⁻⁵⁵
1	C-LD	7. For patients with prosthetic valve endocarditis and relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequent negative blood culture results) without other identifiable source of infection, surgery is recommended. ⁷
1	C-LD	8. In patients with recurrent endocarditis and continued intravenous drug use, consultation with addiction medicine is recommended to discuss the long-term prognosis for the patient's refraining from actions that risk reinfection before repeat surgical intervention is considered. ⁵⁶⁻⁶⁰

Recommendations for Intervention for IE (Continued)		
COR	LOE	Recommendations
2a	B-NR	9. In patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy, early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) is reasonable. ^{53,61-66}
2b	B-NR	10. In patients with native left-sided valve endocarditis who exhibit mobile vegetations >10 mm in length (with or without clinical evidence of embolic phenomenon), early surgery (during initial hospitalization and before completion of a full therapeutic course of antibiotics) may be considered. ^{20,61-63,67}
2b	B-NR	11. In patients with IE and an indication for surgery who have suffered a stroke but have no evidence of intracranial hemorrhage or extensive neurological damage, operation without delay may be considered. ⁶⁸⁻⁷⁰
2b	B-NR	12. For patients with IE and major ischemic stroke with extensive neurological damage or intracranial hemorrhage, if the patient is hemodynamically stable, delaying valve surgery for at least 4 weeks may be considered. ^{68,71}

Synopsis

Management of patients with IE requires a Heart Valve MDT supplemented by inclusion of infectious disease and neurology specialists. The indications for early surgery for patients with IE include HF, persistent infection, abscess, heart block, infection with highly resistant organisms, or recurrent emboli (with persistent vegetations). In patients with implanted electronic devices, infection of the entire system is likely, even if it appears confined to the leads on imaging, and this mandates removal of the entire system to eradicate the infection. In patients with an indication for early surgery, a cerebral embolic event is not a contraindication unless there is extensive neurological damage or intracranial hemorrhage (Figure 16).

Recommendation-Specific Supportive Text

1. IE is best managed in an environment with ready access to specialists in the fields of cardiology, cardiothoracic surgery, and infectious disease, with the option for transfer of complicated cases to a Comprehensive Valve Center when needed. A risk-scoring system using the STS database has been developed to predict surgical risk in patients with IE to help better counsel patients and more objectively define the risks associated with surgery. One trial noted that even when surgery is indicated, women were less likely to undergo a surgical procedure than men (26% versus 47%) and that women had higher in-hospital and 1-year mortality rates than men despite similar comorbidities.^{1,2,4-6}

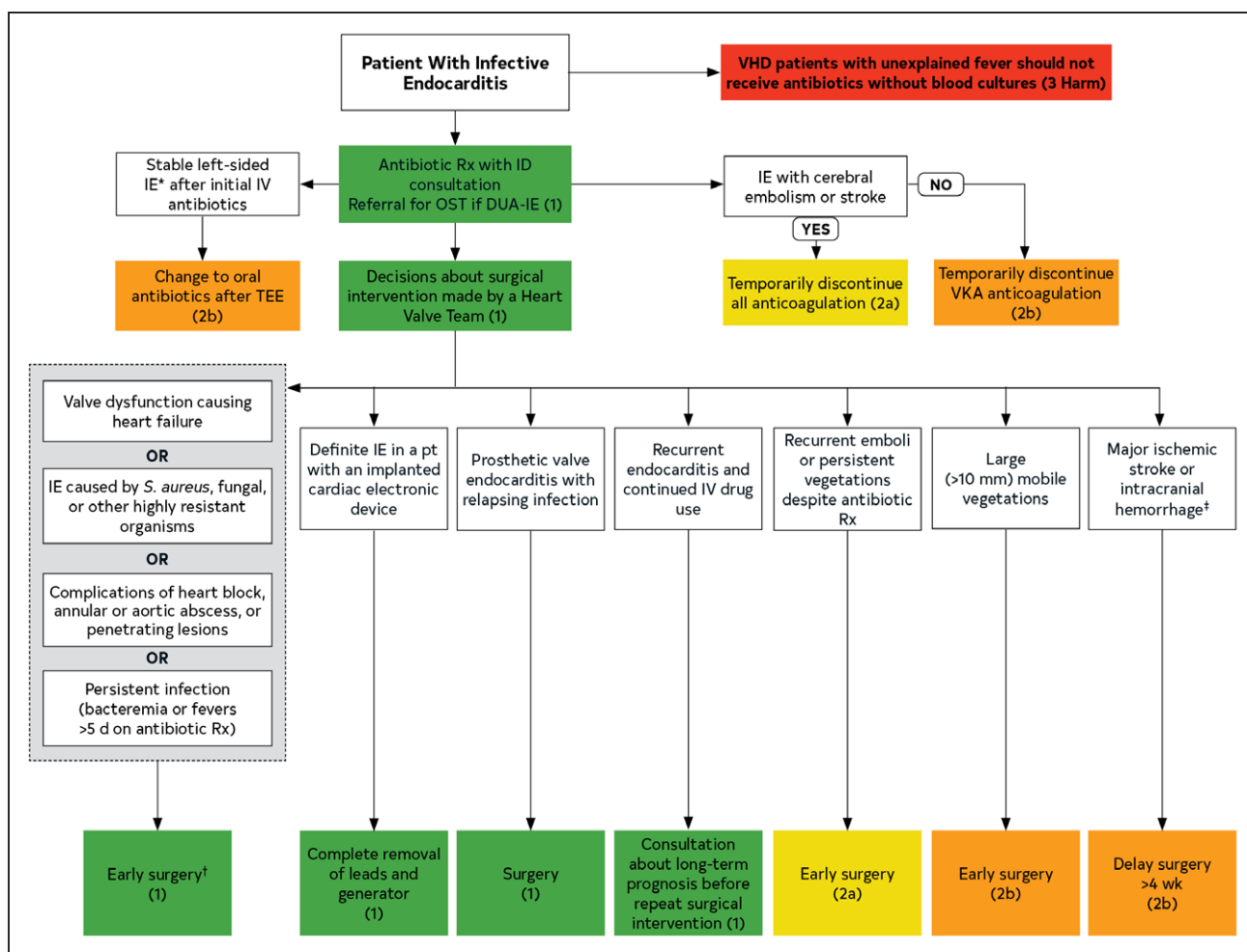


Figure 16. Endocarditis treatment.

Colors correspond to Table 2. *IE caused by streptococcus, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the Heart Valve Team.

†Early surgery defined as during initial hospital course and before completion of a full course of appropriate antibiotics. ‡In patients with an indication for surgery and a stroke but no evidence of intracranial hemorrhage or extensive neurological damage, surgery without delay may be considered. DUA indicates drug use associated endocarditis; HF, heart failure; ICD, implantable cardioverter-defibrillator; ID, infectious disease; IE, infective endocarditis; IV, intravenous; NVE, native valve endocarditis; OST, opioid substitution treatment; pt, patient; PVE, prosthetic valve endocarditis; Rx, therapy; *S. aureus*, *Staphylococcus aureus*; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VHD, valvular heart disease; and VKA, vitamin K antagonist.

- Studies have reported a 21% in-hospital mortality rate in patients with IE and HF who were treated with surgery versus a 45% mortality rate in those who were treated medically. In left-heart native valve endocarditis, 4 baseline features have been independently associated with 6-month mortality: 1) abnormal mental status, 2) moderate to severe HF, 3) bacterial etiology other than *Viridans streptococci*, and 4) medical therapy without valve surgery. Except in injectable drug users, the risk of reinfection after prosthetic valve surgery is low relative to the risk associated with not having surgery in patients with hemodynamic and microbial indications for surgery. Prosthetic valve endocarditis is clearly associated with both higher mortality rates (especially with HF, severe valvular dysfunction, or a staphylococcal or fungal infectious microbe) and higher post-treatment HF-related disability. Surgical series report surgical rates of 50% in patients with prosthetic valve endocarditis, and these patients show improved outcomes over medical therapy, even with controlling for severity of illness at time of diagnosis.^{8,9,15–19}
- Compared with patients with IE attributable to other organisms, patients with left-sided *S. aureus* IE were significantly more likely to die (20% versus 12%), experience an embolic event (60% versus 31%), have a central nervous system event (20% versus 13%), and not undergo surgery (26% versus 39%). Staphylococcal prosthetic valve endocarditis has been associated with a mortality rate as high as 70%, which is driven by resistant staphylococcal species. When *Staphylococcus* is the bacteria, death occurs in <5% of patients with right-sided native valve

endocarditis, which is an important distinction in injectable drug users. Certain pathogens, such as *Pseudomonas aeruginosa*, *Brucella*, fungi, enterococci, and gram-positive cocci are extremely difficult to cure with medical therapy alone and are also prone to abscess or fistula formation and other cardiac tissue destruction. The mortality rate is also significantly lower in patients treated with antifungal agents combined with surgery than in those treated with antifungal agents alone (42% versus 59%).^{9,15,20,22,28–35}

4. Abscess in native valve endocarditis is a life-threatening complication that cannot be cured with antibiotic therapy alone. Extensive paravalvular infections (including annular or aortic abscesses and destructive penetrating lesions or fistulae) are associated with a mortality rate of $\geq 40\%$ and heart block. The long-term results of surgery are very satisfactory, with an actuarial survival rate of $75\% \pm 6\%$ at 5 years. Freedom from recurrent IE has been reported to be 76% at 8 years. Surgical series have shown that the surgical results are related more to a surgeon's ability to remove all infected tissues and reconstruct functional anatomy than to the type of valve used for a replacement. Patients with prosthetic valve endocarditis complicated by paravalvular invasion, as manifested by intracardiac abscesses, fistulae, or heart block, experience high mortality rates and are rarely cured by medical treatment alone. By contrast, surgical series have reported surgical survival rates of 71% in this high-risk group.^{9,41–44}
5. Blood culture samples will typically become negative after 48 hours of appropriate antimicrobial therapy, except for with methicillin-resistant *S. aureus* and other resistant organisms, for which it may take up to a week for cultures to become negative. Some caution is advised in patients who develop recurrent fever after an initially successful response to antibiotics because the fever could be explained by reasons other than the endocarditic valve. Ongoing infection despite antibiotic therapy is common with aggressive microorganisms, resulting in abscess formation, valve destruction, fistulas, or large vegetations.^{7,9,15,46,48}
6. Optimal therapy for cardiac device IE combines complete device extraction and a prolonged course of parenteral antibiotics with complete device and lead removal, even if evidence for infection appears to be limited to the generator pocket site. A prospective cohort study using data from the ICE-PCS (International Collaboration on Endocarditis–Prospective Cohort Study) showed that among patients with cardiac device IE, the rates of both concomitant valve infection and mortality are high, particularly if there is valve dysfunction. A proportional hazards regression analysis showed a survival benefit at 1 year for device removal during the initial hospitalization; 28 of 141 patients (19.9%) who underwent device removal during the index hospitalization had died at 1 year, versus 13 of 34 (38.2%) who did not undergo device removal (HR: 0.42; 95% CI: 0.22–0.82).^{49,54,55,72}
7. Relapsing infections may be caused by incomplete sterilization of valvular or paravalvular tissue secondary to a deep tissue infection. Even in the absence of other indications for intervention, such as severe valve dysfunction or a resistant organism, if there is no other source for persistent bacteremia, heart valve infection must be presumed to be the source. If the source of infection is uncertain, additional imaging with PET/CT may be helpful in decision-making.⁷
8. The incidence of drug use–associated IE continues to rise, with a known risk of IE that is 100-fold higher than that of the general population. In a National Institutes of Health–sponsored statewide health survey in the state of North Carolina, 42% of all IE valve surgeries performed between 2007 and 2017 were undertaken in patients with injection drug use–related IE. The care of these patients is associated with longer hospital stays, higher readmission rates, higher rates of recurrent IE, and higher costs of care. With evolving science in addiction medicine, there is evidence that referral to addiction therapy can reduce mortality and morbidity rates in these patients. In patients admitted with drug use–associated endocarditis, addiction specialists are an integral part of the MDT.^{56–60}
9. Embolic events are associated with increased morbidity and mortality in IE and occur in 20% to 40% of patients with IE. The risk of embolism is highest during the first days after initiation of antibiotic treatment and decreases after 2 weeks. Embolic incidence decreases to 9% to 21% after initiation of antibiotic treatment. Factors associated with a new embolic event are vegetation size >10 mm and marked vegetation mobility (especially when associated with the anterior leaflet of the mitral valve). Early surgery is associated with a reduction in the rate of embolic complications in patients who present with left-sided IE, severe VHD, and large vegetations (>10 mm).^{53,61,64–66}
10. With native valve endocarditis, large vegetation size is associated with a markedly higher rate of embolic phenomena. In an RCT of surgical intervention in patients with severe left-sided valve dysfunction and vegetations >10 mm in

length (even in the absence of clinically apparent embolic events or HF), there was no significant difference in all-cause mortality rate at 6 months in the early surgery versus the conventional treatment groups (3% and 5%, respectively; $P=0.59$); however, there was a marked reduction in the number of embolic events: 0% in the early surgery group compared with 21% in the conventional treatment group ($P=0.005$). Additionally, 77% of the conventional treatment group required surgery during the initial hospitalization or during the follow-up phase secondary to HF, paravalvular extension, and heart block.^{20,61}

11. Stroke is an independent risk factor for postoperative death in patients with IE. Recommendations about the timing of operative intervention after a stroke in the setting of IE are hindered by the lack of RCTs and reliance on single-center experiences. In early observational data, there was a significantly decreased risk of in-hospital death when surgery was performed >4 weeks after the stroke.⁷³ These data were not risk adjusted. In an observational study that did adjust for factors such as age, paravalvular abscess, and HF, the risk of in-hospital death was not significantly higher in the group who underwent surgery within a median time from admission to operation of 5 days, with only a 1% risk of perioperative hemorrhagic conversion.^{68–70,74}
12. Patients with hemorrhagic stroke and IE have a prohibitively high surgical risk for at least 4 weeks after the hemorrhagic event. One multicenter observational study⁷¹ showed wide variation in patient deaths when those who underwent surgery within 4 weeks of a hemorrhagic stroke were compared with those whose surgery was delayed until after 4 weeks (75% versus 40%, respectively). The percentage of new postoperative bleeds was 50% in patients whose surgery was performed in the first 2 weeks, 33% in patients whose surgery was performed in the third week, and 20% in patients whose surgery was performed at least 21 days after the neurological event.⁶⁸

13. PREGNANCY AND VHD

The physiological hemodynamic changes associated with pregnancy are usually well tolerated in women with structurally normal hearts. However, for women with VHD, the hemodynamic burden may pose significant challenges during pregnancy and delivery.

13.1. Initial Management of Women With VHD Before and During Pregnancy

Recommendations for Initial Management of Women With VHD Before and During Pregnancy

Referenced studies that support the recommendations are summarized in Online Data Supplement 43.

COR	LOE	Recommendations
1	B-NR	1. Women with suspected valve disease who are considering pregnancy should undergo a clinical evaluation and TTE before pregnancy. ^{1–5}
1	B-NR	2. Women with severe valve disease (Stages C and D) who are considering pregnancy should undergo pre-pregnancy counseling by a cardiologist with expertise in managing women with VHD during pregnancy. ^{1–5}
1	B-NR	3. Pregnant women with severe valve disease (Stages C and D) should be monitored in a tertiary-care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists, and maternal-fetal medicine obstetricians with expertise in the management of high-risk cardiac conditions during pregnancy. ^{1–12}
2a	B-NR	4. In asymptomatic women with severe valve disease (Stage C1) who are considering pregnancy, exercise testing is reasonable before pregnancy for risk assessment. ^{3–5,11,13–15}

Synopsis

To assure the best possible outcome for a woman with VHD and her baby, a comprehensive evaluation is best performed before the time of conception. During pregnancy, the frequency and intensity of follow-up and treatment are heavily dependent on the type and severity of valve lesion, as well as patient symptoms.

Recommendation-Specific Supportive Text

1. The risks to the mother and fetus during pregnancy are highly dependent on the type and severity of valve disease. Clinical evaluation of women with VHD who are contemplating pregnancy includes a complete TTE with full anatomic and hemodynamic assessment of the valves.^{1–5} A congenital bicuspid or unicuspid aortic valve is often associated with dilation of the aortic sinuses, the ascending aorta, or both. Evaluation of women with a congenitally abnormal aortic valve includes assessment of the aorta before pregnancy because of the risk of further aortic enlargement and aortic dissection during pregnancy.^{1–5}
2. Pre-pregnancy counseling with a cardiologist experienced with managing women with valve disease during pregnancy allows discussion of the risks of pregnancy for the mother and fetus. A complete assessment of functional capacity, severity of valve lesions, status of the LV and RV, and pulmonary

pressures is necessary to determine the risk of pregnancy and delivery. Medications are reviewed to avoid agents that may have potential harmful effects on the fetus. Pre-pregnancy evaluation also allows discussion of options for interventions before pregnancy, such as valve replacement, valve repair, or percutaneous aortic or mitral balloon dilation, particularly in those patients with severe rheumatic MS or AS.¹⁻⁵

3. Women with severe valve disease who become pregnant are at an elevated risk of cardiac morbidity and mortality. Babies born to such mothers are also at risk of serious complications. Identification and management of complications are improved by monitoring in a tertiary-care center with an experienced team of healthcare providers who have expertise in managing high-risk cardiac conditions during pregnancy.¹⁻¹²
4. Patients with severe valve disease may be asymptomatic, which can pose a diagnostic and therapeutic dilemma in women with these disorders who are considering pregnancy. Exercise testing is reasonable to assist with risk assessment in patients in whom it is unclear whether pregnancy can be tolerated without an intervention to repair or replace the valve before pregnancy.^{3-5,11,13-15} Symptoms provoked by exercise testing are synonymous with spontaneous symptoms. Patients who develop symptoms on exercise testing should be treated as having symptomatic valve disease (Stage D), and should undergo pre-pregnancy counseling by a cardiologist with expertise in managing women with VHD during pregnancy

13.1.1. Medical Therapy for Women With VHD Before and During Pregnancy

Recommendations for Medical Therapy of Pregnant Women With VHD		
Referenced studies that support the recommendations are summarized in Online Data Supplement 43.		
COR	LOE	Recommendations
2a	C-LD	1. In pregnant women with VHD, beta-blocker medications are reasonable as required for heart rate control or treatment of arrhythmias. ¹⁻⁶
2a	C-LD	2. In pregnant women with VHD and HF symptoms (Stage D), diuretic medications are reasonable if needed for volume overload. ^{7,8}
3: Harm	B-NR	3. In pregnant women with VHD, ACE inhibitors and ARBs should not be given because of fetal risk. ^{6,9-11}

Synopsis

Women with severe VHD are at risk of HF, arrhythmia, and other cardiac disorders during pregnancy. Although

medical therapy may be necessary to preserve the mother's health, there may be negative consequences for the fetus. Therefore, the fetal effects of cardiac medications must be understood so that the appropriate risks and benefits can be weighed.¹⁻⁶ Data from ROPAC (Registry On Pregnancy And Cardiac Disease), a large multicenter registry supported by the European Society of Cardiology, showed an association between the use of cardiac medications during pregnancy and adverse fetal outcome. This association was attributable, in part, to the associated maternal cardiac diseases that required the medications.⁶ Anticoagulation for pregnant women with AF should conform to the guidelines in nonpregnant patients.^{12,13} Recommendations for anticoagulation regimens during pregnancy are discussed in section 13.2.2.

Recommendation-Specific Supportive Text

1. Beta-blocker medications are used to control heart rate or to treat arrhythmias. However, maternal use of beta blockers has been associated with a newborn birth weight approximately 100 g lower than that of newborns whose mothers did not take beta blockers.⁶ The use of beta blockers with beta-1 selectivity avoids the beta-2 effects on uterine relaxation. The incidence of fetal growth retardation is lower with metoprolol treatment than with atenolol treatment in pregnancy.¹⁻⁶
2. Diuretic medications can alleviate the effects of volume overload in pregnant women with VHD and HF symptoms (Stage D). However, reduction of volume overload must be balanced against the reduction in placental blood flow associated with diuretic medications.^{7,8} Additionally, data from ROPAC suggested that maternal diuretic use was associated with rates of low birth weight and fetal mortality that were higher than for women not taking any medications. In part, this association was attributable to the severity of the underlying HF requiring treatment.^{7,8}
3. ACE inhibitors and ARBs are strongly associated with fetal malformations when used by women during pregnancy.⁹⁻¹¹

13.1.2. Intervention for Women With Native VHD Before and During Pregnancy

13.1.2.1. Pre-Pregnancy Intervention

Recommendations for Pre-Pregnancy Intervention in Women With VHD		
Referenced studies that support the recommendations are summarized in Online Data Supplement 43.		
COR	LOE	Recommendations
1	B-NR	1. In symptomatic women with severe VHD who are considering pregnancy, intervention before pregnancy is recommended on the basis of standard indications. ¹⁻¹¹

Recommendations for Pre-Pregnancy Intervention in Women With VHD (Continued)		
COR	LOE	Recommendations
1	C-EO	2. In women who require a valve intervention before pregnancy, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences, including discussion of the risks of mechanical valves during pregnancy and the reduced durability of bioprosthetic valves in young women.
2a	C-LD	3. In asymptomatic women with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage C1) who are considering pregnancy, PMBC at a Comprehensive Valve Center is reasonable before pregnancy for those who have favorable valve morphology. ^{1-5,12,13}
2a	B-NR	4. In women of childbearing age who require valve replacement, bioprosthetic valves are preferred over mechanical valves because of the increased maternal and fetal risks of mechanical heart valves in pregnancy. ¹⁴
2a	C-EO	5. In asymptomatic women with severe AS (aortic velocity ≥ 4.0 m/s or mean pressure gradient ≥ 40 mm Hg, Stage C) who are considering pregnancy, valve intervention before pregnancy is reasonable.
2b	C-EO	6. In asymptomatic women with severe AS (aortic velocity ≥ 4.0 m/s or mean pressure gradient ≥ 40 mm Hg, Stage C1) who are considering pregnancy, do not meet COR 1 criteria for intervention, and have a preconception evaluation confirming the absence of symptoms (including normal exercise stress testing and serum BNP measurements), medical management during pregnancy may be considered to avoid prosthetic valve replacement.
2b	C-EO	7. In asymptomatic women with severe MR (Stage C1) and a valve suitable for repair who are considering pregnancy, valve repair before pregnancy at a Comprehensive Valve Center may be considered but only after detailed discussion with the patient about the risks and benefits of the surgery and its effect on future pregnancies.

Synopsis

In women with severe VHD who are considering pregnancy, the indications for considering intervention include the presence of symptoms, asymptomatic severe AS, asymptomatic severe MR with a repairable valve, and asymptomatic severe rheumatic MS with a valve morphology suitable for PMBC. If a prosthetic valve is needed, the shared decision-making process about the choice of type of prosthetic valve should include discussion of the risks of valve thrombosis and adverse effects from anticoagulation with mechanical valves versus the reduced durability of bioprosthetic valves in young women (Figure 17).

Recommendation-Specific Supportive Text

1. Standard indications for intervention in symptomatic patients with severe valve disease also apply to women who are considering pregnancy.¹⁻¹¹

2. Women of childbearing age who require valve intervention have important choices to make about the risks and benefits of the types of prosthetic valves. The risks to the mother and fetus of valve thrombosis and anticoagulation during pregnancy with a mechanical valve must be weighed against the reduced durability of bioprosthetic valves in young women. For women considering a mechanical prosthesis, it has been proposed that they undergo a preoperative trial of anticoagulation with warfarin to assess the dose needed to achieve a target INR. In 1 small study, women who required <5 mg daily of warfarin and then underwent subsequent mechanical AVR did not experience maternal or fetal complications during pregnancy.¹⁵ Larger trials are needed, however, before this becomes standard practice. Shared decision-making with a cardiologist with expertise in the management of severe valve disease during pregnancy allows discussion of these issues in women of childbearing age before valve surgery, even when pregnancy is not planned in the near future.^{1,14,16}
3. Severe rheumatic MS presents a significant risk of maternal adverse outcome during pregnancy. In asymptomatic women with severe rheumatic MS (mitral valve area ≤ 1.5 cm², Stage C) and favorable valve morphology who are considering pregnancy, PMBC results in an increase in mitral valve area and reduction in transmitral gradient, which makes the patient more resilient to the hemodynamic load of pregnancy.^{1-5,12,13}
4. Pregnant women with a bioprosthetic valve, compared with women with a mechanical valve who are on anticoagulation, have a lower risk of valve thrombosis, excessive bleeding, and fetal and maternal death.¹⁴ The Ross procedure is an alternative if performed in women with favorable anatomy and at centers with expertise in the procedure.
5. Most patients with mild to moderate AS can tolerate the hemodynamic changes of pregnancy without cardiovascular events. Patients with severe AS are at an increased risk of complications, with HF developing in 10% to 44% of patients and arrhythmias in up to 25%, even if they were asymptomatic before pregnancy. Progressive as well as sudden deterioration may occur during pregnancy and delivery in patients with severe AS. Fetal complications are frequent also. Options for relief of valvular AS in young women include percutaneous aortic balloon dilation in patients with noncalcified congenital AS, the Ross procedure, or a surgical bioprosthetic or mechanical valve. TAVI has not been studied in young women, and few data

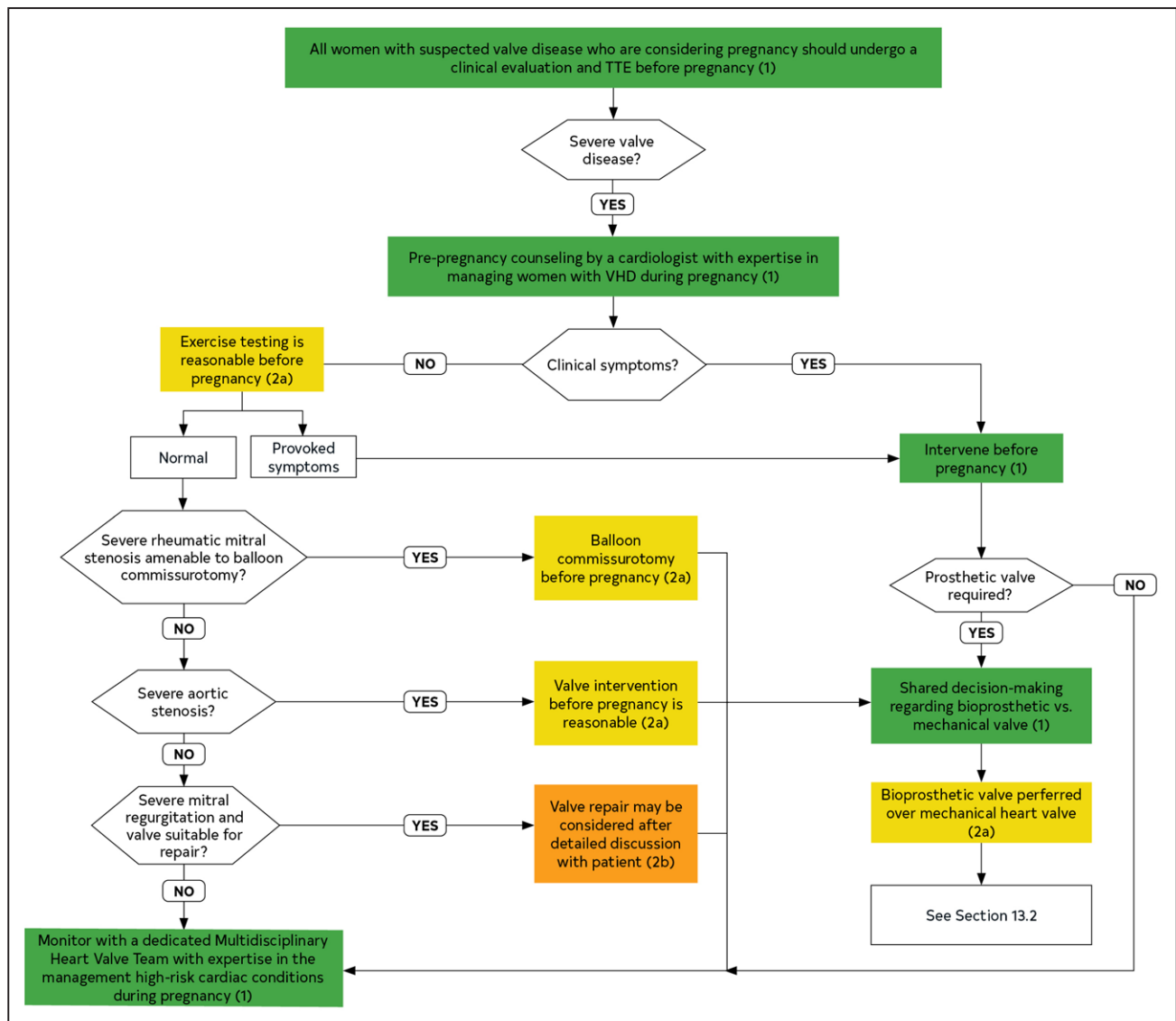


Figure 17. Preconception management of women with native valve disease.

Colors correspond to Table 2. TTE indicates transthoracic echocardiography; and VHD, valvular heart disease.

exist on outcomes with this valve type during pregnancy.^{1,3,6–10}

6. Some women with severe asymptomatic AS, normal LV systolic function, and normal biomarkers may choose to undergo pregnancy without valve intervention. The risks of deterioration during pregnancy must be balanced against the risk of mechanical valve complications during pregnancy or the long-term risks of a bioprosthetic valve in a young patient. In experienced centers, these women can often be treated with activity restriction, volume management, and optimization of loading conditions.^{1,3,6–10}
7. The threshold for valve operation for valve regurgitation is higher in the asymptomatic patient who might ever become pregnant than

in patients who will not become pregnant because there always is the possibility that valve repair will not be successful and a prosthetic valve will be needed. Most patients with asymptomatic severe MR tolerate the hemodynamic changes of pregnancy, and there is no evidence for acceleration of LV dysfunction during pregnancy. High-risk features for development of HF during pregnancy in women with MR include depressed LV systolic function and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg). In high-risk asymptomatic women with severe MR, referral to a Comprehensive Valve Center allows consideration of mitral valve morphology, the likelihood of a successful valve repair, and estimated surgical risk in the decision-making process.^{1,11,16}

13.1.2.2. During-Pregnancy Intervention

Recommendations for Intervention During Pregnancy in Women With VHD		
Referenced studies that support the recommendations are summarized in Online Data Supplement 43.		
COR	LOE	Recommendations
2a	B-NR	1. In pregnant women with severe AS (mean pressure gradient ≥ 40 mm Hg, Stage D), valve intervention during pregnancy is reasonable if there is hemodynamic deterioration or if there are NYHA class III or IV HF symptoms. ¹⁻⁷
2a	B-NR	2. In pregnant women with severe rheumatic MS (mitral valve area ≤ 1.5 cm ² , Stage D) and with valve morphology favorable for PMBC who remain symptomatic with NYHA class III or IV HF symptoms despite medical therapy, PMBC is reasonable during pregnancy if it is performed at a Comprehensive Valve Center. ⁸⁻¹²
2a	C-LD	3. In pregnant women with severe valve regurgitation and with NYHA class IV HF symptoms (Stage D) refractory to medical therapy, valve surgery is reasonable during pregnancy. ¹³⁻¹⁶
3: Harm	C-LD	4. In pregnant women with VHD, valve surgeries should not be performed in the absence of severe HF symptoms refractory to medical therapy. ¹³⁻¹⁶

Synopsis

In pregnant women with severe VHD who develop severe, intractable symptoms despite maximal medical therapy, surgical or percutaneous intervention may become necessary.

Recommendation-Specific Supportive Text

1. Patients with severe AS may develop progressive HF or sudden hemodynamic deterioration during the stress of pregnancy. Both open heart surgery and percutaneous balloon dilation of the aortic valve are high-risk procedures during pregnancy for both the mother and the fetus and should be performed only if there is hemodynamic deterioration or if there are severe NYHA class III or IV HF symptoms. The type of intervention will be dependent on the valve morphology and on the expertise of the center. The intervention should always be performed in a center with a multidisciplinary group of cardiologists, interventionalists, cardiac anesthesiologists, and obstetricians specializing in high-risk obstetrics.^{1-7,9-12}
2. Patients with severe rheumatic MS may develop progressive HF or sudden hemodynamic deterioration during the hemodynamic stress of pregnancy. Percutaneous balloon dilation of the mitral valve is a high-risk procedure during pregnancy for both the mother and the fetus and should be performed only if there is hemodynamic deterioration or if there are severe NYHA class III or IV HF symptoms.¹⁷⁻¹⁹ The

intervention will also be dependent on an acceptable valve morphology. The intervention should always be performed in a center with a multidisciplinary group of cardiologists, interventionalists, cardiac anesthesiologists, and obstetricians specializing in high-risk obstetrics.^{1-7,9-12,20}

3. Regurgitant valve lesions are generally better tolerated during pregnancy than are stenotic ones. Valve surgery is reasonable only in the rare pregnant woman with severe valve regurgitation with NYHA class IV HF symptoms refractory to medical therapy.¹³⁻¹⁶
4. Valve surgery during pregnancy is high risk, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate reported. It should be reserved only for patients with severe, intractable symptoms unresponsive to bed rest and maximally tolerated medical therapy.¹³⁻¹⁶

13.2. Prosthetic Valves in Pregnant Women

13.2.1. Initial Management

Recommendations for Initial Management of Prosthetic Heart Valves in Pregnant Women		
Referenced studies that support the recommendations are summarized in Online Data Supplement 44.		
COR	LOE	Recommendations
1	C-EO	1. Women with a prosthetic valve should undergo pre-pregnancy assessment, including echocardiography, by a cardiologist with expertise in managing women with VHD during pregnancy.
1	C-EO	2. Pregnant women with a mechanical prosthesis should be monitored in a tertiary-care center with a dedicated MDT of cardiologists, surgeons, anesthesiologists, and maternal-fetal medicine obstetricians with expertise in the management of high-risk cardiac conditions during pregnancy. ¹⁻³
1	B-NR	3. Women with mechanical heart valves considering pregnancy should be counselled that pregnancy is high risk and that there is no anticoagulation strategy that is consistently safe for the mother and baby. ³⁻⁶
1	B-NR	4. Pregnant women with a mechanical prosthetic valve who have prosthetic valve obstruction or experience an embolic event should undergo a TEE. ⁷⁻⁹

Synopsis

Pregnancy in women with mechanical heart valves is very high risk and has been classified by the World Health Organization as Risk Category III (significantly increased risk of maternal mortality or severe morbidity). Contemporary studies and prospective registries of pregnancy in women with mechanical heart valves confirm that maternal risk remains high: Maternal mortality rate is approximately 1%, and the risk of valve thrombosis is approximately 5%.^{2,5,9} Given the substantial risk of adverse maternal and fetal

events, there is a need for specialized expertise in the counseling and care of women with prosthetic heart valves who are considering pregnancy or who are pregnant.

Recommendation-Specific Supportive Text

1. A preconception TTE is used to assess valve function, ventricular function, and pulmonary artery systolic pressure. Preconception TTE can help identify women with valve dysfunction who may benefit from valve intervention before conception. Results can facilitate patient counseling about specific risks of pregnancy.
2. The management of prosthetic heart valves during pregnancy is substantially different from the management of prosthetic heart valves in a nonpregnant patient. There is a much higher risk of mechanical valve thrombosis during pregnancy because of the hypercoagulable state. Choosing the appropriate anticoagulation strategy to balance risks to the mother and fetus requires a team familiar with management of prosthetic heart valves in pregnancy to provide comprehensive counseling. The management of anticoagulation also requires specialized expertise, and frequent titration of VKA or heparin doses is needed.^{2,10} Transvalvular gradients increase during pregnancy because of increased heart rate, plasma volume, and stroke volume.¹ In the event that valve intervention is required during pregnancy, the comprehensive Heart Valve Team and maternal-fetal medicine team is required to optimize maternal and fetal outcomes.
3. Each anticoagulation strategy has relative advantages and disadvantages in terms of maternal and fetal safety, but there is no anticoagulation strategy that is consistently safe for the mother and fetus. The maternal mortality rate is >1%, and serious maternal and fetal complications are common, even with modern mechanical heart valves and careful management.⁴⁻⁶ After counseling, some women with mechanical heart valves may choose not to become pregnant, whereas others may wish to proceed with pregnancy, so comprehensive and candid counseling about the risks of pregnancy with a mechanical heart valve is important.
4. Pregnancy is a time of increased risk of mechanical valve thrombosis, so there should be high suspicion of valve thrombosis in women with an embolic event, clinical deterioration, symptoms of HF, or a pronounced increase in valve gradients or valve regurgitation during pregnancy. TEE is useful to visualize leaflet motion and thrombus burden. Fluoroscopy and gated cardiac CT are also useful in evaluating patients with suspected valve thrombosis.^{7,11,12}

13.2.2. Anticoagulation for Pregnant Women With Mechanical Prosthetic Heart Valves

Recommendations for Anticoagulation for Pregnant Women With Mechanical Prosthetic Heart Valves		
Referenced studies that support the recommendations are summarized in Online Data Supplement 48.		
COR	LOE	Recommendations
1	B-NR	1. Pregnant women with mechanical prostheses should receive therapeutic anticoagulation with frequent monitoring during pregnancy. ¹⁻¹⁰
1	B-NR	2. Women with mechanical heart valves who cannot maintain therapeutic anticoagulation with frequent monitoring should be counseled against pregnancy. ^{7,8,10-15}
1	B-NR	3. Women with mechanical heart valves and their providers should use shared decision-making to choose an anticoagulation strategy for pregnancy. Women should be informed that VKA during pregnancy is associated with the lowest likelihood of maternal complications but the highest likelihood of miscarriage, fetal death, and congenital abnormalities, particularly if taken during the first trimester and if the warfarin dose exceeds 5 mg/d. ^{3-6,11,14,16}
1	C-LD	4. Pregnant women with mechanical valve prostheses who are on warfarin should switch to twice-daily LMWH (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL at 4 to 6 hours after dose) or intravenous UFH (with an activated partial thromboplastin time [aPTT] 2 times control) at least 1 week before planned delivery. ^{5,8,13,17-20}
1	C-LD	5. Pregnant women with mechanical valve prostheses who are on LMWH should switch to UFH (with an aPTT 2 times control) at least 36 hours before planned delivery. ¹⁹⁻²¹
1	C-LD	6. Pregnant women with valve prostheses should stop UFH at least 6 hours before planned vaginal delivery. ¹⁹⁻²¹
1	C-LD	7. If labor begins or urgent delivery is required in a woman therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation. ^{3,22,23}
2a	B-NR	8. For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, continuation of warfarin for all 3 trimesters is reasonable after full discussion with the patient about risks and benefits. ^{3,6,16,18,22,24,25}
2a	B-NR	9. For pregnant women with mechanical prostheses who require >5 mg/d of warfarin to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day during the first trimester, followed by warfarin during the second and third trimesters, is reasonable. ^{3,6,15,16,25}
2a	B-NR	10. For pregnant women with mechanical prostheses who require a dose of warfarin >5 mg/d to achieve a therapeutic INR, and for whom dose-adjusted LMWH is unavailable, dose-adjusted continuous intravenous UFH during the first trimester (with aPTT 2 times control), followed by warfarin for the second and third trimesters, is reasonable. ^{3,6,11,16}

Recommendations for Anticoagulation for Pregnant Women With Mechanical Prosthetic Heart Valves (Continued)		
COR	LOE	Recommendations
2a	B-NR	11. For hemodynamically stable pregnant women with obstructive left-sided mechanical valve thrombosis, it is reasonable to manage with slow-infusion, low-dose fibrinolytic therapy. ²⁶
2b	B-NR	12. For pregnant women with mechanical prostheses who require a warfarin dose >5 mg/d to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day for all 3 trimesters may be considered. ^{3,6,14-16,27}
2b	B-NR	13. For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, dose-adjusted LMWH at least 2 times per day during the first trimester, followed by warfarin for the second and third trimesters, may be considered. ^{1-3,6,12,16,22}
2b	B-NR	14. For pregnant women with mechanical prostheses, aspirin 75 to 100 mg daily may be considered, in addition to anticoagulation, if needed for other indications. ²⁸
3: Harm	B-NR	15. For pregnant women with mechanical prostheses, LMWH should not be administered unless anti-Xa levels are monitored 4 to 6 hours after administration and dose is adjusted according to levels. ^{8-10,15,27}
3: Harm	B-R	16. For patients with mechanical valve prostheses, anticoagulation with the direct thrombin inhibitor, dabigatran, should not be administered. ²⁹
3: Harm	C-EO	17. The use of anti-Xa direct oral anticoagulants with mechanical heart valves in pregnancy has not been assessed and is not recommended. ³⁰⁻³²

Synopsis

Pregnant women with mechanical heart valves are at increased risk of serious maternal complications, including valve thrombosis, thromboembolism, hemorrhage, and death. The risk of poor fetal outcomes is also high, with increased rates of spontaneous abortion, fetal death, fetal hemorrhage, and teratogenicity related to VKAs. For women with mechanical heart valves, the maternal mortality rate remains >1%. More than one-third of women with mechanical heart valves have a serious maternal or fetal complication during pregnancy.^{1-4,9,24,33,34}

All women with mechanical heart valves require uninterrupted therapeutic anticoagulation throughout pregnancy. The choice of anticoagulation strategy is challenging because there are inherent trade-offs between maternal safety and fetal safety. Warfarin is the most effective anticoagulant at preventing thrombotic complications, but warfarin crosses the placenta and can cause miscarriage, spontaneous abortion, warfarin embryopathy, or fetal intracranial hemorrhage.

Although LMWH is not teratogenic, women with mechanical heart valves on LMWH are at increased risk of thrombotic events, particularly when LMWH is improperly dosed, monitored, or administered. There is no single optimal anticoagulation strategy that suits all women.

There are 3 potential strategies: 1) Continue warfarin throughout pregnancy; 2) use heparin throughout pregnancy; and 3) use sequential therapy, with heparin during the first trimester and warfarin during the second and third trimesters (Figure 18).

Recommendation-Specific Supportive Text

1. The risk of catastrophic valve failure or stroke is prohibitively high for women with mechanical heart valves who cannot take dose-adjusted and frequently monitored anticoagulation throughout pregnancy.¹⁻¹⁰
2. Much of the maternal morbidity and mortality during pregnancy occurs in women who are not receiving appropriate doses of anticoagulation because of improper administration, improper monitoring, or medication nonadherence. Women who are not able to receive therapeutic anticoagulation or do not have access to frequent monitoring and dose adjustment are at prohibitive risk for pregnancy.¹³⁻¹⁵
3. No anticoagulation strategy is optimally safe for both the mother and the fetus. Warfarin is safest for the mother but crosses the placenta and can cause fetal intracranial hemorrhage; fetal loss; and teratogenicity, particularly at doses >5 mg/d and when given during the first trimester, keeping in mind that the warfarin dose needed to maintain a therapeutic INR may change during pregnancy. Neither UFH nor LMWH crosses the placenta, but each is associated with higher rates of maternal complications than are seen with warfarin.^{3,4,6,16,18,20,23,25,35,36} Depending on a woman's values and priorities, she may choose an anticoagulation strategy that minimizes maternal risk, minimizes fetal risk, or attempts to achieve a balance between maternal and fetal risk. Physicians should not assume a woman's values or preferences, nor should physicians supplant their own preferences for those of the patient. Counseling and shared decision-making allows for a woman and her physician to choose the best anticoagulation to achieve the woman's goals.
4. Warfarin crosses the placental barrier and results in anticoagulation of the fetus, as well as the mother. There is a higher risk of fetal intracranial hemorrhage if the mother is fully anticoagulated with warfarin during vaginal delivery. Women taking warfarin can minimize the risk

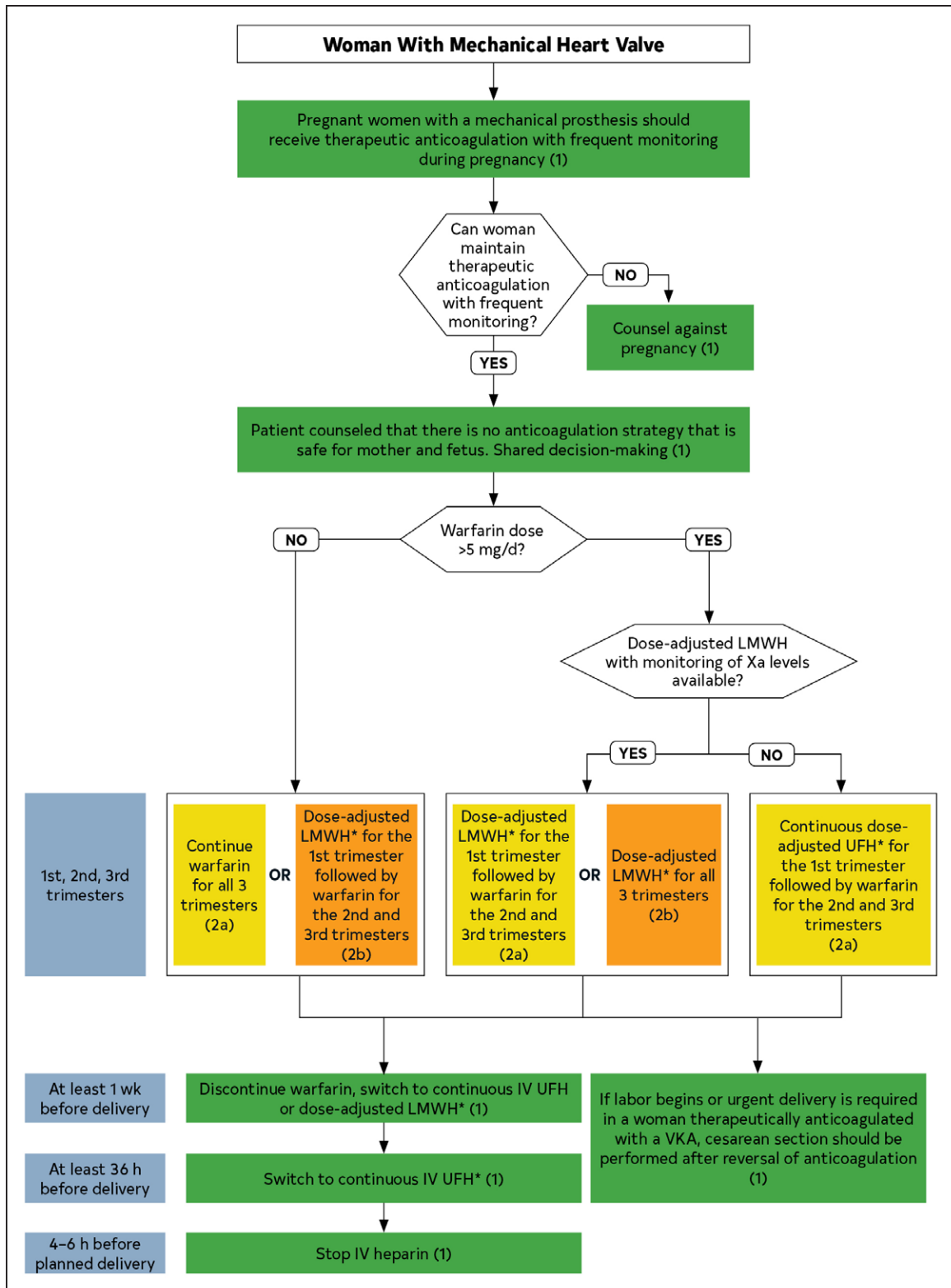


Figure 18. Anticoagulation for prosthetic mechanical heart valves in women during pregnancy.

Colors correspond to Table 2. *Dose-adjusted LMWH should be given at least 2 times per day, with close monitoring of anti-Xa levels. Target to Xa level of 0.8 to 1.2 U/mL, 4 to 6 hours after dose. Trough levels may aid in maintaining patient in therapeutic range. Continuous UFH should be adjusted to aPTT 2 times control. aPTT indicates activated partial thromboplastin time; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

- by switching to a heparin preparation before planned delivery.^{5,8,13,17–20}
5. Although LMWH does not result in an anticoagulated fetus, the risk of maternal hemorrhage is high if delivery occurs while the mother is on LMWH. Therefore, it is recommended that the mother be hospitalized before planned delivery, with discontinuation of long-acting anticoagulation and initiation of intravenous continuous infusion of UFH to keep aPTT >2 times control levels.^{19,20}
 6. Intravenous heparin should be stopped long enough before delivery to reduce risk of maternal bleeding and allow safe placement of epidural anesthesia (typically at least 6 hours). Exact timing should be coordinated with the obstetrics and anesthesia teams.^{19,20}
 7. Because warfarin results in an anticoagulated fetus, there is a high risk of fetal intracranial hemorrhage if vaginal delivery is attempted in a woman who is anticoagulated with warfarin. If a woman goes into labor while on warfarin, appropriate reversal of anticoagulation followed by cesarean section reduces the risk of fetal intracranial hemorrhage.^{3,22,23}
 8. The teratogenic effects of warfarin are dose dependent. The rate of warfarin embryopathy is reduced (<3%) but not eliminated if the daily dose of warfarin is ≤5 mg/d.^{3,6,16,18,23,25,36,37} In most women, the effective dose of warfarin typically does not vary significantly during pregnancy.³⁸ For women who require a dose ≤5 mg/d, continuation of low-dose warfarin throughout pregnancy poses the lowest combined risk to mother and fetus.^{3,6,16} The number of reported pregnancies on low-dose warfarin is relatively small, and not all publications have found improved fetal outcomes on low-dose warfarin,¹¹ so caution should be exercised until more data are available.
 9. If warfarin is taken in doses >5 mg/d during the first trimester of pregnancy, there is a >30% risk of fetal loss or embryopathy. For women who require >5 mg/d to maintain a therapeutic INR, replacing warfarin with dose-adjusted LMWH during the first trimester reduces fetal loss.^{3,6,10,15,16,23,39,40} While the patient is taking LMWH, anti-Xa levels should be monitored at least weekly and the dose adjusted accordingly. Fixed dosing is never appropriate, because it is associated with high maternal morbidity and mortality.⁴¹ After the first trimester, the fetal toxicity of warfarin is substantially lower, so switching back to warfarin for the second and third trimesters results in a reasonable balance between maternal safety and fetal safety.
 10. In regions where LMWH is unavailable or cost-prohibitive, or if anti-Xa levels cannot be monitored, continuous infusion of UFH can be used as an alternative to LMWH during the first trimester for women who require a warfarin dose of >5 mg/d.³⁷ If UFH is used during the first trimester, the dose should be adjusted to maintain an aPTT 2 times control. There are several disadvantages to UFH compared with LMWH: Women are at greater risk for line infections, osteoporosis, and heparin-induced thrombocytopenia, so UFH should be reserved for situations where dose-adjusted LMWH is not feasible.¹⁰ Intermittent subcutaneous injection of UFH is not an acceptable alternative because it is associated with prohibitive rates of valve thrombosis.⁴² UFH is associated with very high rates of valve thrombosis, stroke, and death in pregnant women with mechanical heart valves during the second and third trimesters.^{3,4,43}
 11. In carefully selected women with thrombosis of a mechanical heart valve during pregnancy, low-dose, slow-infusion, tissue-type plasminogen activator (tPA) can be an alternative to surgical valve replacement. Women who are optimal candidates are hemodynamically stable and have obstructive prosthetic valve thrombosis, valve thrombosis with embolic complications, or nonobstructive valve thrombosis with a thrombus >10 mm.⁴⁴ Given the high rates of fetal loss with cardiac surgery during pregnancy, thrombolysis is an attractive alternative for appropriately selected, hemodynamically stable women with mechanical valve thrombosis.
 12. Although the teratogenicity of warfarin is highest during the first trimester, there is still a risk of pregnancy loss or fetal hemorrhage when warfarin is taken during the second and third trimesters. Therefore, after appropriate counseling, some women may choose to avoid warfarin entirely throughout pregnancy. For these women, dose-adjusted LMWH throughout pregnancy is the safest alternative. LMWH throughout pregnancy is associated with a higher rate of thrombotic complications than warfarin. However, many of the thrombotic events occur when LMWH is administered improperly or monitored erratically or if patients are nonadherent.^{8,14,15,39} When administered and monitored meticulously, LMWH can be safe.¹² Effective dose monitoring includes weekly measurements of anti-factor Xa levels, with additional monitoring after dose adjustment.¹³ Measurement of trough levels to maintain a trough Xa level >0.6 IU/mL may help women maintain therapeutic anticoagulation while on LMWH.^{12,13}
 13. When warfarin is taken at a dose ≤5 mg/d, the risk of warfarin embryopathy is reduced but not entirely eliminated. Some women, after discussion with their physicians, may choose to substitute

LMWH for low-dose warfarin during the first trimester to eliminate the risk of warfarin embryopathy. This choice improves fetal outcomes but at the cost of increased maternal thrombotic complications.^{1–3,12}

14. Low-dose aspirin is regarded as safe during pregnancy and can be continued in women with mechanical heart valves if needed for other indications. There may be noncardiac indications for aspirin in pregnant women, such as prevention of preeclampsia.²⁸
15. Studies using subcutaneous LMWH at a fixed dose without monitoring of anti-Xa levels in pregnant patients with mechanical prostheses found a high risk of valve thrombosis and maternal death. In pregnant women treated with dose-adjusted LMWH, the dose of LMWH required to maintain an adequate anti-Xa level 4 to 6 hours after administration increases throughout pregnancy.^{9,15,39,41}
16. A randomized clinical trial of dabigatran in non-pregnant patients with mechanical heart valves showed an increased rate of thromboembolic and bleeding complications with dabigatran compared with warfarin.⁴⁵ The safety and effectiveness of anti-Xa direct oral anticoagulants has not been established in patients with mechanical heart valves. Additionally, the safety of anti-Xa direct oral anticoagulants in pregnancy is unknown.^{30–32}
17. Anti-Xa direct oral anticoagulants have not been shown to be safe in patients with mechanical heart valves, so they should not be used in pregnancy.

14. SURGICAL CONSIDERATIONS

Concomitant surgical procedures may be appropriate at the time of intervention for VHD in the interest of reducing periprocedural risk (eg, treatment of significant CAD) or for optimizing long-term outcomes (eg, adding a maze procedure for AF treatment). Consideration may also be given to treating moderate disease in the interest of obviating the need for subsequent reoperation—for example, treating aortic dilation in the presence of a BAV. This is particularly true when one can anticipate particular difficulty in the conduct of a subsequent reoperation, as may be the case for mitral valve intervention after AVR or in a patient with prior mediastinal irradiation for whom postoperative adhesions are often severe. The benefits of such concomitant procedures must be balanced against the potential impact on periprocedural risk due to added complexity. In particular, interventions that add significantly to aortic cross-clamp time may be discouraged in patients with poor LV function or significant pulmonary hypertension. Prolongation of cardiopulmonary bypass time may increase renal injury, particularly among those with preexisting renal

dysfunction. More complex procedures may also pose a particular risk in patients with fragile tissue integrity or general frailty, and the additional dissection that may be required in a reoperative setting may tip the balance away from imposing additional risk by performing concomitant procedures.

14.1. Evaluation and Management of CAD in Patients With VHD

14.1.1. Management of CAD in Patients Undergoing TAVI

Recommendations for Management of CAD in Patients Undergoing TAVI

Referenced studies that support the recommendations are summarized in Online Data Supplement 45.

COR	LOE	Recommendations
1	C-EO	1. In patients undergoing TAVI, 1) contrast-enhanced coronary CT angiography (in patients with a low pretest probability for CAD) or 2) an invasive coronary angiogram is recommended to assess coronary anatomy and guide revascularization.
2a	C-LD	2. In patients undergoing TAVI with significant left main or proximal CAD with or without angina, revascularization by PCI before TAVI is reasonable. ^{1,2}
2a	C-LD	3. In patients with significant AS and significant CAD (luminal reduction >70% diameter, fractional flow reserve <0.8, instantaneous wave-free ratio <0.89) consisting of complex bifurcation left main and/or multivessel CAD with a SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score >33, SAVR and CABG are reasonable and preferred over TAVI and PCI. ^{3,4}

Synopsis

CAD is common among patients presenting with AS, particularly the elderly. In the surgical experience, concomitant revascularization impacts long-term survival in a favorable way and is commonplace, as is preoperative coronary imaging. Similarly, there is an argument to be made for coronary revascularization among patients undergoing TAVI, although the effects on late outcomes are less well defined and may not be the same as for SAVR, given the different demographics and comorbidities of the TAVI versus SAVR populations. Nonetheless, at this point, diagnostic imaging and consideration of revascularization are appropriate (Figure 19).

Recommendation-Specific Supportive Text

1. The prevalence of CAD in patients with severe AS ranges between 15% and 80%.⁵ and varies depending on the definition of CAD used and the populations examined.⁶ The impact of CAD on outcomes is controversial,^{7,8} although one report

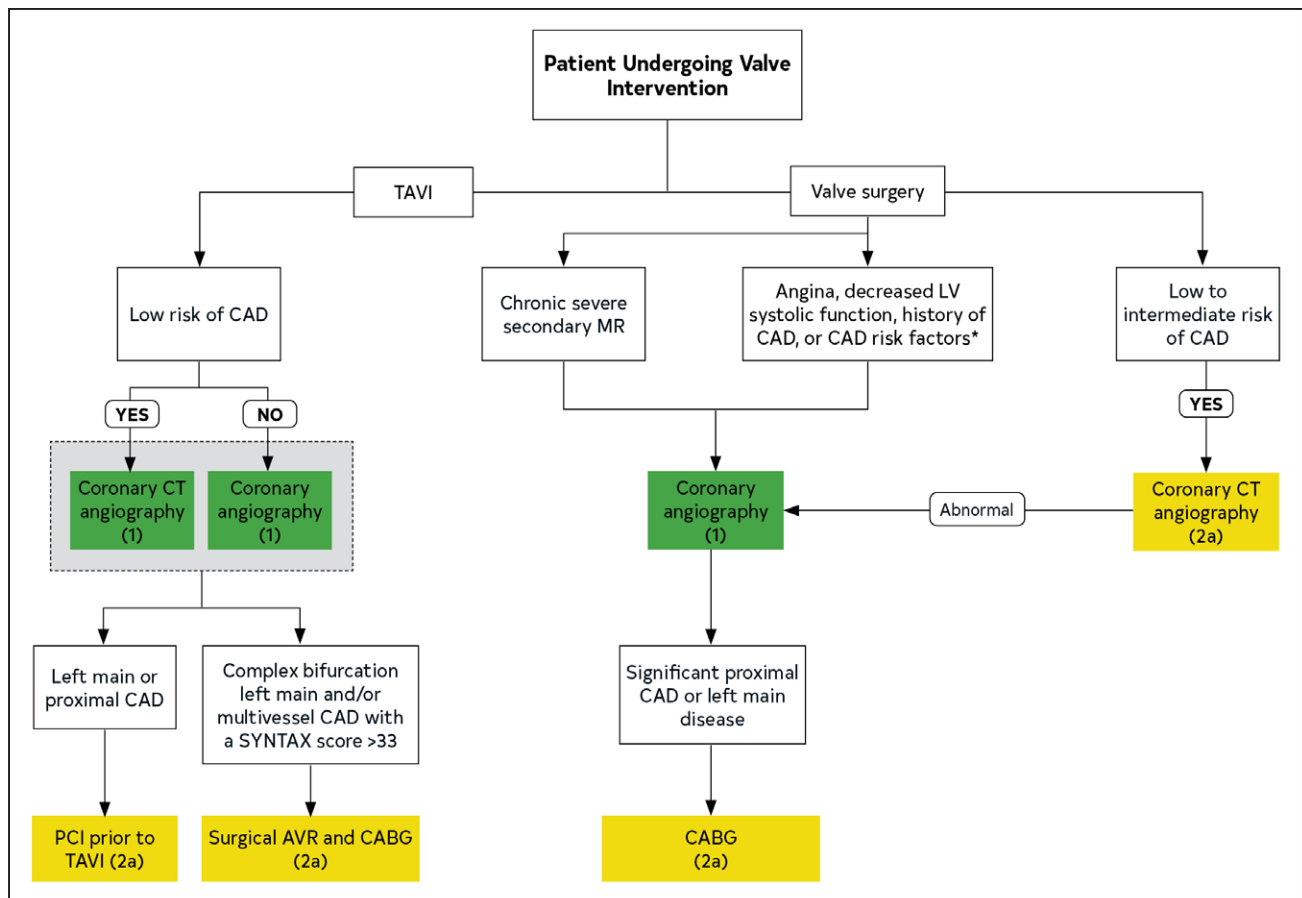


Figure 19. Management of CAD in patients undergoing valve interventions.

Colors correspond to Table 2. *Including men age >40 years and postmenopausal women. AVR indicates aortic valve replacement; CAD, coronary artery disease; CABG, coronary artery bypass graft; CT, computed tomography; LV, left ventricular; MR, mitral regurgitation; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and TAVI, transcatheter aortic valve implantation.

singled out severe CAD (defined by a SYNTAX score >22) and incomplete revascularization as the only independent predictors of death after TAVI.⁹ Assessment of the coronary anatomy is important in patients with severe AS to rule out obstructive CAD. Invasive coronary angiography is commonly performed. In patients with a low pretest probability of CAD, contrast-enhanced coronary CT angiography¹⁰ has an excellent negative predictive value.^{11,12} In patients with normal renal function, an option is to combine contrast-enhanced coronary CT angiography with CT assessment of the peripheral circulation and heart structure as an initial imaging test, reserving coronary angiography for the event that the contrast-enhanced coronary CT angiography is nondiagnostic or significant CAD is found. Invasive functional assessment of coronary lesions in TAVI candidates by using fractional flow reserve or instantaneous wave-free ratio is safe and feasible.^{13–15} Instantaneous wave-free ratio may be particularly attractive because it does not require the administration of a vasodilator and is less influenced by the effect of the

stenotic aortic valve, although randomized clinical trials validating the utility of both are ongoing.

- There are no RCTs to inform clinical practice on the benefits and timing of PCI in patients undergoing TAVI. The decision to perform PCI is therefore driven by myriad clinical factors (eg, presence of angina or ischemia, ability to take dual-antiplatelet therapy before TAVI) and anatomic factors (eg, lesion location and complexity, technical feasibility) and should be individualized. Overall, nonrandomized studies suggest that PCI before TAVI is safe and feasible,¹ even in patients with left main disease.² Conceptually, pre-TAVI PCI also allows a safer procedure and circumvents future post-TAVI PCI, which can be occasionally challenging. Staged PCI before TAVI is a common strategy in clinical practice and is associated with lower contrast volume and renal failure than is the strategy of TAVI with concomitant PCI,¹ although the timing of pre-TAVI PCI remains controversial.
- Multiple RCTs have been conducted to define the optimal management of CAD in patients without VHD based on the SYNTAX score to define

those least amenable to percutaneous treatment. Subsets of patients shown to have superior freedom from major adverse cardiac events include those with complex left main disease and those with a SYNTAX score >33.³ Accordingly, a surgical approach is reasonable in this subset of patients. Among SAVR patients, revascularization for those with significant CAD (>50% stenosis) has been shown to impact late risk of mortality favorably.⁴

14.1.2. Management of CAD in Patients Undergoing Valve Surgery

Recommendations for Management of CAD in Patients Undergoing Valve Surgery		
Referenced studies that support the recommendations are summarized in Online Data Supplement 45.		
COR	LOE	Recommendations
1	C-LD	1. In patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men >40 years of age and postmenopausal women), invasive coronary angiography is indicated before valve intervention. ¹⁻⁸
1	C-LD	2. In patients with chronic severe secondary MR, invasive coronary angiography should be performed as part of the evaluation. ⁹⁻¹¹
2a	B-NR	3. In selected patients with a low to intermediate pretest probability of CAD, contrast-enhanced coronary CT angiography is reasonable to exclude the presence of significant obstructive CAD. ¹²⁻¹⁸
2a	C-LD	4. In patients undergoing valve repair or replacement with significant proximal CAD (≥70% reduction in luminal diameter in major coronary arteries or ≥50% reduction in luminal diameter in the left main coronary artery and/or physiologically significance), CABG is reasonable for selective patients. ^{19,20}

Synopsis

Coronary imaging in the setting of VHD defines anatomy that may be at risk during surgery or intervention. Given their similar demographic profiles, CAD and VHD frequently coexist, and in the case of secondary MR they have a pathophysiological link. Revascularization, in turn, can impact periprocedural risk or long-term outcome. In the case of secondary MR, revascularization may positively impact the valve disease via reverse remodeling of the LV. In the surgical setting, where repeat intervention is at high cost to the patient, efforts are typically made to correct all surgically correctable disease present at the index operation. Accordingly, an aggressive approach to revascularization is appropriate. In the setting of percutaneous interventions, however, the option of sequential interventions with interval tests of improvement may be appropriate. In either case, less invasive imaging via contrast-enhanced coronary CT angiography is increasingly adopted.

Recommendation-Specific Supportive Text

- CAD is frequently present among patients with VHD¹⁻⁴ and may contribute to angina pectoris among those with aortic valve disease.^{3,4} Knowledge of coronary anatomy contributes to risk stratification, in addition to directing concomitant coronary revascularization. There is a very low prevalence of CAD among men <40 years of age and premenopausal women with no atherosclerotic risk factors^{2,5-7} or history of mediastinal radiation.⁸
- Functional MR occurs in patients with structurally normal valve leaflets and chordae because of LV dysfunction, including regional wall motion abnormalities or global dilation with displacement of the papillary muscles, leaflet tethering, annular dilation, and decreased closing forces from reduced contractility.⁹⁻¹¹ Because this LV dysfunction may be attributable to CAD and accompanying myocardial ischemia, the assessment of coronary anatomy status is necessary to complete the diagnosis and allow evaluation of revascularization options.
- Contrast-enhanced coronary CT angiography is an alternative to coronary angiography among selected patients who are at low to intermediate pretest probability of CAD before valve surgery.¹² This does not include patients who have active symptoms of angina, those with documented ischemia, or those with a prior history of CAD, all of whom should have selective coronary angiography. Recent studies, most often in the setting of a pre-TAVI evaluation, have demonstrated diagnostic sensitivity of >90%, specificity of 60% to 90%,^{13-15,21} and accuracy of >90%.²¹ Contrast-enhanced coronary CT angiography may be safer than coronary angiography in selected patient populations, such as those with IE and vegetations on the aortic valve. However, a positive contrast-enhanced coronary CT angiogram, defined as the presence of epicardial CAD, requires confirmation with invasive coronary angiography to establish the need for and extent of CABG. The risk of radiation exposure and renal failure because of the contrast injection should be taken into consideration.
- The presence of uncorrected CAD has been shown to negatively impact both perioperative^{22,23} and late outcomes of surgery for VHD.¹⁹ Accordingly, concomitant CABG has been favored. These studies of concomitant CABG at the time of valve surgery have demonstrated little or no adverse impact on the acute perioperative mortality rate, despite increased cross-clamp and cardiopulmonary bypass times. Moreover, combined CABG

and valve surgery reduces the rate of perioperative myocardial infarction, and incomplete revascularization is associated with greater postoperative LV systolic dysfunction and a reduced survival rate after surgery as compared with patients who receive complete revascularization. For more than a decade, improved myocardial preservation techniques have been associated with reduced overall operative mortality rates, and it has become standard practice to bypass all significant coronary artery stenoses, when possible, in patients undergoing valve surgery. In patients with a significant stenosis of the left anterior descending artery, a left internal thoracic artery graft should be used if possible. Hybrid PCI followed by surgical valve repair or replacement has been reported favorably but is restricted to patients at high risk with a combined surgical approach.²⁰

14.2. Intervention for AF in Patients With VHD

Recommendations for Intervention for AF in Patients With VHD Referenced studies that support the recommendations are summarized in Online Data Supplement 46.		
COR	LOE	Recommendations
1	C-LD	1. In patients with VHD and AF for whom surgical intervention is planned, the potential symptomatic benefits and additional procedural risks of adjunctive arrhythmia surgery at the time of cardiac valvular surgery should be discussed with the patient. ¹⁻¹¹
2a	B-R	2. For symptomatic patients with paroxysmal or persistent AF who are undergoing valvular surgery, surgical pulmonary vein isolation or a maze procedure can be beneficial to reduce symptoms and prevent recurrent arrhythmias. ^{1,2,12-15}
2a	B-NR	3. For patients with AF or atrial flutter who are undergoing valve surgery, LA appendage ligation/excision is reasonable to reduce the risk of thromboembolic events. ¹⁶⁻¹⁹
2a	B-NR	4. In patients undergoing LA surgical ablation of atrial arrhythmias and/or LA appendage ligation/excision, anticoagulation therapy is reasonable for at least 3 months after the procedure. ²⁰⁻²²
3: Harm	B-NR	5. For patients without atrial arrhythmias who are undergoing valvular surgery, LA appendage occlusion/excision/amputation is potentially harmful. ²³

Synopsis

For patients undergoing valve surgery with symptomatic AF or atrial flutter, concomitant maze procedure with or without atrial appendage occlusion/excision/amputation is a proven treatment for the atrial arrhythmia but requires postoperative anticoagulation for at least 3 months after the procedure (Figure 20).

Recommendation-Specific Supportive Text

1. Surgical ablations, including pulmonary vein isolation and atrial maze at the time of valvular surgery and other open cardiac operations, have been demonstrated in multiple studies to reduce the recurrence of AF.⁵⁻¹¹ Various approaches to pulmonary vein isolation and modified left atrial, right atrial, and bi-atrial maze procedures entail longer procedure times, with higher risks of operative complications and permanent pacemaker implantation.¹⁻⁴ These adverse outcomes, coupled with the lack of large randomized trial data confirming mortality and stroke benefit, should be examined with the patient.
2. The atrial maze procedure properly refers to a specific bi-atrial lesion set performed by a “cut-and-sew” technique or with tissue ablation technologies, including cryoenergy or radiofrequency. Of note, the term “maze” is often loosely applied to many variations of the original lesion set that may be less effective. When performed with complete encirclement of the pulmonary veins, most commonly in combination with mitral valve repair or replacement but also with aortic or tricuspid valve procedures, the maze procedure affords freedom from AF with an efficacy similar to that of catheter-based approaches.^{1,2,12-15} Patients undergoing combined atrial maze procedure at the time of operation for MR have a greater freedom from recurrent AF than those who did not have a maze procedure.¹¹ In patients with recurrent AF who are to undergo surgical correction of MR, catheter ablation is best deferred in favor of a concomitant surgical maze, thereby avoiding the potential complications of a catheter maze and a second procedure for the patient.
3. A reduction in thromboembolism has been demonstrated by LA ligation/excision, although the benefit is less evident in those patients who maintain anticoagulation.¹⁶⁻¹⁹ Discontinuation of oral anticoagulation has also been associated with late stroke, highlighting that the LA appendage is not the exclusive source of all thrombi in patients with AF. Therefore, there are insufficient data to support routine discontinuation of anticoagulation in patients with AF who are undergoing LA ligation/excision.
4. Ablation with radiofrequency/cryoenergy or atrial suture lines provides an endocardial thrombogenic milieu, and in addition, surgical LA appendage occlusion can be incomplete.²⁰⁻²² In the context of atrial arrhythmias, manipulation of the LA, and post-cardioversion/defibrillation stunning, atrial mechanical function can be slow to recover. The resultant stasis and thrombogenic endocardial lesions provide a nidus for thrombus development, placing this group of patients at

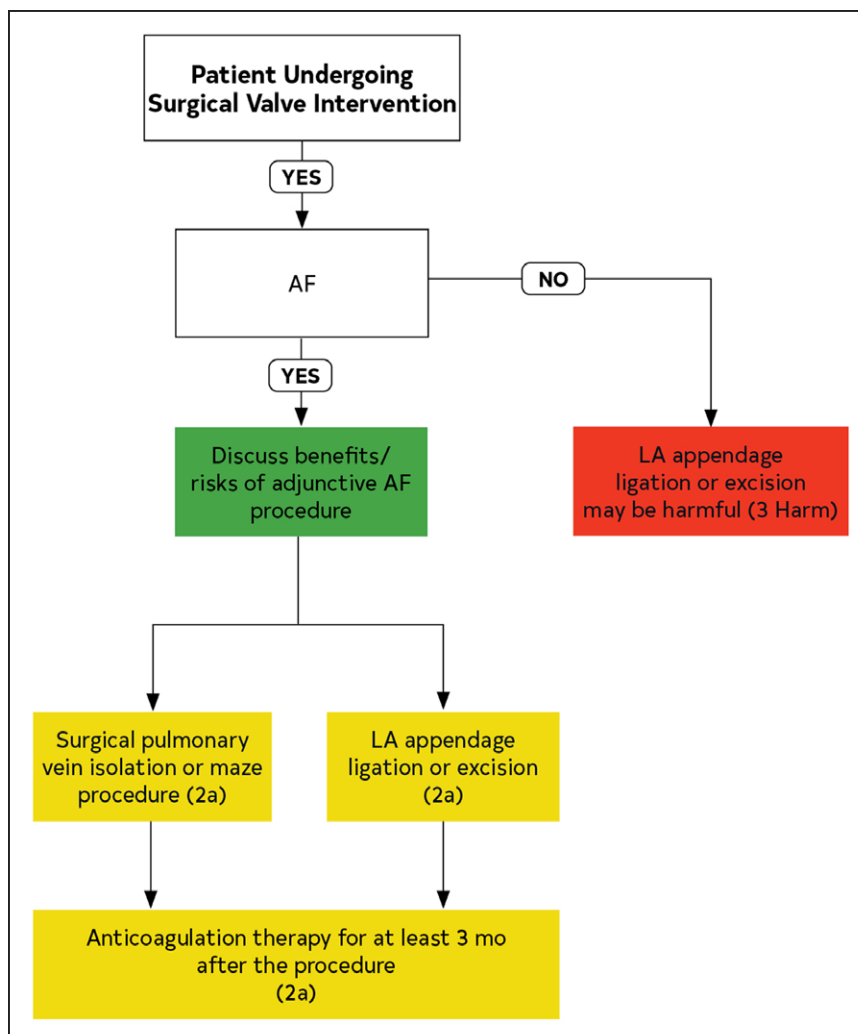


Figure 20. Intervention for AF in patients with VHD.

Colors correspond to Table 2. AF indicates atrial fibrillation; LA, left atrial, and VHD, valvular heart disease.

risk of stroke. Nonrandomized registry data indicate that stroke in the first 3 months after catheter ablation is driven chiefly by discontinuation of oral anticoagulation.²¹ Both US and European guideline statements on catheter ablation recommend (on the basis of expert opinion alone) anticoagulation during this periprocedural phase while the endocardium heals from the ablation. By analogy, patients who have had surgical ablation should be managed with at least 3 months of anticoagulation, regardless of their CHA₂DS₂-VASc risk score. Subsequent anticoagulation should be based on evaluation of arrhythmia recurrence in the context of their CHA₂DS₂-VASc score. Anticoagulation should also be given for at least 3 months after LA ligation/excision. For patients receiving bioprostheses, a VKA would be the preferred method of anticoagulation for the first 3 months (see Section 2.4.3).

5. A higher incidence of early AF in all patients after LA appendage occlusion/excision has been demonstrated.²³ Together with the recognition that

most patients do not develop AF after surgery, pre-emptive LA appendage occlusion in patients without preexisting AF cannot be recommended. No stroke benefit has been observed in this group of patients with no pre-emptive history of AF.

15. NONCARDIAC SURGERY IN PATIENTS WITH VHD

15.1. Diagnosis of Patients With VHD Undergoing Noncardiac Surgery

Recommendation for Diagnosis in Patients With VHD Undergoing Noncardiac Surgery		
COR	LOE	Recommendation
1	C-EO	1. In patients with clinically suspected moderate or greater degrees of valvular stenosis or regurgitation who are undergoing noncardiac surgery, preoperative echocardiography is recommended.

Synopsis

The evaluation of patients with VHD who are undergoing noncardiac surgery is dependent on the type and

severity of VHD, including 1) the presence or absence of symptoms, 2) the severity of VHD, 3) the risk of noncardiac intervention, 4) the response of the LV and/or RV to the overload caused by VHD, and 5) the pulmonary artery systolic pressure. If the patient meets standard criteria for a cardiac intervention, it is prudent to defer elective noncardiac procedures and proceed to valve intervention first.¹⁻⁴ However, in emergency situations, noncardiac surgery may be necessary in the presence of uncorrected severe valve disease. All patients with severe VHD who are undergoing noncardiac surgery benefit from an evaluation by a Heart Team consisting of a cardiologist, cardiac anesthesiologist, and cardiac surgeons, in conjunction with the surgeon performing the procedure. In patients with severe VHD who are undergoing low-risk surgical procedures or in patients with mild to moderate VHD, noninvasive monitoring in consultation with a cardiovascular anesthesiologist may be all that is needed. In patients with severe VHD who are undergoing elevated-risk noncardiac surgery, decisions should be made as to whether to proceed with the noncardiac surgery and whether invasive hemodynamic or TEE imaging monitoring should be performed intraoperatively and postoperatively in an intensive care setting.

Recommendation-Specific Supportive Text

1. After a careful clinical evaluation and preoperative resting 12-lead ECG, patients being evaluated for noncardiac surgery who have known or suspected VHD of moderate or greater degree benefit from TTE.⁵ If there has been no change in clinical course, an echocardiogram within the past 12 months can be used. Most adverse events have occurred because the diagnosis of VHD was not known to the surgical team. The echocardiographic evaluation should quantify the severity of valve stenosis or regurgitation, calculate systolic function, estimate diastolic function, evaluate LV size and myocardial structure, estimate RV size and function, and estimate pulmonary artery systolic pressure.⁴ AS is present in 1% to 2% of all patients >65 years of age and 3% to 8% of all patients >75 years of age. Severe AS is associated with an increased risk during noncardiac surgery, depending on the specific degree of valve narrowing, LV systolic function, concurrent CAD, type of surgery, and other risk factors associated with surgery. Rheumatic MS may also be poorly tolerated during the altered hemodynamics of anesthesia and noncardiac surgery. Left-sided regurgitant lesions are better tolerated but still convey increased risk, particularly if the anesthesiologist and surgeon are unaware of the diagnosis or severity of valve disease.

15.2. Management of the Symptomatic Patient

Recommendation for Management of the Symptomatic Patient With VHD Undergoing Noncardiac Surgery

COR	LOE	Recommendation
1	C-EO	1. In patients who meet standard indications for intervention for VHD (replacement and repair) on the basis of symptoms and disease severity, intervention should be performed before elective noncardiac surgery to reduce perioperative risk if possible, depending on the urgency and risk of the noncardiac procedure. ¹

Synopsis

Symptomatic patients with severe VHD benefit from valve intervention before noncardiac surgery, if possible.

Recommendation-Specific Supportive Text

1. Noncardiac surgery patients with symptomatic severe AS have the highest risk of cardiac complications; the estimated rate of cardiac complications in patients with undiagnosed severe AS undergoing noncardiac surgery is 10% to 30%. AVR (SAVR, TAVI) performed before elective elevated-risk noncardiac surgery in symptomatic patients with severe AS will prevent hemodynamic instability during, as well as after, noncardiac surgery.¹⁻⁷ In AS patients who are undergoing noncardiac surgery, there is lack of data on the efficacy or safety of TAVI,⁸ but TAVI is a reasonable option to avoid delay of semi-urgent noncardiac surgery. In hemodynamically unstable patients at high to prohibitive surgical risk for AVR, balloon aortic valvuloplasty as a bridging strategy may be an option.⁹⁻¹¹ Symptomatic patients with rheumatic MS (the pathophysiology and implications of rheumatic MS and AS are similar) or patients with pulmonary artery systolic pressure >50 mmHg benefit from valvular intervention before elective noncardiac surgery according to recommendations for rheumatic MS. Left-sided regurgitant lesions also convey increased cardiac risk during noncardiac surgery.^{1,2} Although these lesions are generally better tolerated than stenotic valvular disease, in patients with MR and AR who are undergoing elective elevated-risk (ie, intermediate- or high-risk) noncardiac surgery and who meet standard indications for intervention, mitral or aortic valve surgery (repair or replacement) optimally should be performed before noncardiac surgery.

15.3. Management of the Asymptomatic Patient

Recommendations for Management of the Asymptomatic Patient With VHD Undergoing Noncardiac Surgery		
Referenced studies that support the recommendations are summarized in Online Data Supplement 47.		
COR	LOE	Recommendations
2a	B-R	1. In asymptomatic patients with moderate or greater degrees of AS and normal LV systolic function, it is reasonable to perform elective noncardiac surgery. ¹⁻³
2a	C-EO	2. In asymptomatic patients with moderate or greater degrees of rheumatic MS with less than severe pulmonary hypertension (pulmonary artery systolic pressure <50 mm Hg), it is reasonable to perform elective noncardiac surgery.
2a	C-LD	3. In asymptomatic patients with moderate or greater degrees of MR and normal LV systolic function with less than severe pulmonary hypertension (pulmonary artery systolic pressure <50 mm Hg), it is reasonable to perform elective noncardiac surgery. ⁴⁻⁷
2a	C-LD	4. In asymptomatic patients with moderate or greater degrees of AR and normal LV systolic function, it is reasonable to perform elective noncardiac surgery. ⁸

Synopsis

In asymptomatic patients with significant VHD who do not meet standard criteria for intervention, the risk associated with the noncardiac procedure can be minimized by choosing an anesthetic approach that is appropriate to the valve lesion and ensuring a higher level of intraoperative (and perioperative) monitoring, taking into account the underlying valvular abnormality, its effect on LV function, and comorbidities. In patients with VHD, the cardiovascular risk of noncardiac surgery is also impacted by other cardiovascular conditions, such as LV and RV dysfunction, CAD, pulmonary hypertension, and peripheral artery disease. In patients with moderate or greater degrees of AS, the hemodynamic effects of anesthesia and surgery are poorly tolerated; predictors of adverse outcomes include severity of AS, coexisting MR, pulmonary hypertension, and CAD. However, these comorbidities also increase the risk of AVR. Data are limited, but the risk–benefit ratio continues to favor managing asymptomatic patients with severe AS who are undergoing noncardiac surgery with hemodynamic monitoring and optimization of loading conditions, rather than considering prophylactic AVR. The patient with rheumatic MS who is undergoing noncardiac surgery is treated in a manner similar to the patient with AS. Regurgitant lesions also convey an increased risk of cardiac complications in patients undergoing noncardiac surgery and thus require careful evaluation and hemodynamic monitoring.

Recommendation-Specific Supportive Text

1. Asymptomatic patients with severe AS and a normal LVEF can undergo noncardiac surgery with acceptable risk, particularly in the absence of severe CAD.¹⁻³ Thus, pre-operative evaluation to exclude severe CAD with CT or angiographic imaging may be useful. In these patients with severe asymptomatic AS, cardiac complications can be reduced by periprocedural continuous optimization of loading conditions, thereby avoiding hypotension and tachycardia. Sinus rhythm with normal heart rate should be maintained. Tachycardia and systemic hypotension may result in decreased coronary perfusion pressure, development of arrhythmias or ischemia, myocardial injury, cardiac failure, or death. Periprocedural hemodynamic monitoring with a right-heart catheter or intraoperative TEE may be particularly useful to allow continuous optimization of loading conditions. Intraoperative and postoperative monitoring of blood pressure and intracardiac volume are implemented starting in the preoperative period and continuing until hemodynamics are stable, up to 24 to 48 hours after the procedure. General anesthetics are well tolerated, and the anesthetic agents should be chosen to maintain sinus rhythm and normotension. Phenylephrine or norepinephrine can be used to increase blood pressure in patients with no significant CAD.^{9,10} In case of systemic hypertension, arterial dilators, such as short-acting calcium channel blockers, are preferred. Epidural or spinal anesthetic interventions should be modified to avoid rapid changes in systemic pressure, using only high-dilution neuraxial local anesthetic agents in combination with opioids.¹¹⁻¹⁴
2. In asymptomatic patients with moderate or greater degrees of rheumatic MS with a pulmonary artery systolic pressure <50 mm Hg, elevated-risk noncardiac surgery can be performed with invasive hemodynamic monitoring to optimize loading conditions. Maintenance of LV preload and sinus rhythm should be the targets in the perioperative period. Preload should be maintained at a level high enough to allow an adequate forward cardiac output across the stenotic mitral valve but low enough to avoid pulmonary edema. Preload attainment can be challenging and requires measurement of cardiac output and pulmonary wedge pressure. Of particular concern is judicious intravenous fluid administration, so as to avoid increases in the LA pressure and pulmonary capillary pressure that may precipitate

acute pulmonary edema. Tachycardia should be avoided because of the shortened diastolic LV filling time across the stenotic mitral valve, resulting in an increase in LA pressure.^{15–17} In asymptomatic patients with significant rheumatic MS and with a pulmonary artery systolic pressure >50 mm Hg, the risk of elective intermediate- to high-risk noncardiac surgery is considerably higher, so these patients should be evaluated and treated as outlined in the rheumatic MS section (Section 6.2).^{6,7,18}

3. In asymptomatic patients with significant MR and normal LV systolic function with a pulmonary artery systolic pressure <50 mm Hg who are undergoing elective noncardiac surgery, the overall hemodynamic goals are avoidance of both increased afterload and bradycardia by choosing the appropriate anesthetic scheme. Left-sided regurgitant lesions convey chronic LV volume overload and increased cardiac risk during noncardiac surgery but are better tolerated than is stenotic valvular disease.¹¹ Patients with significant MR undergoing noncardiac surgery had higher rates of postoperative HF and myocardial infarction than did controls without MR.⁴ The combination of neuraxial local anesthetics and opioids produces a favorable systemic vasodilation for patients with regurgitant valve lesions. Patients with regurgitant lesions will also do well with general anesthesia, which also lowers systemic vascular resistance. However, preload should be maintained.^{15,16} Invasive hemodynamic and/or intraoperative TEE monitoring allows for continuous optimization of LV filling pressures and LV function during and after the operative procedure. Patients should be admitted to an intensive monitoring setting for up to 24 to 72 hours after the procedure.¹⁵ In functional MR, especially in these patients for whom very careful attention to afterload control and fluid balance is crucial, anesthetic considerations should also include management of the underlying heart disease (ie, ischemic heart disease, hypertrophic cardiomyopathy).
4. Patients with severe AR are prone to hemodynamic instability because of the detrimental effects of increased volume on myocardial wall stress. The perioperative stress associated with noncardiac surgery may lead to hypotension, arrhythmias, HF, or even death. Patients with significant AR undergoing noncardiac surgery had a higher in-hospital mortality rate and higher morbidity rate, including postoperative myocardial infarction, stroke, pulmonary edema, intubation

>24 hours, and major arrhythmias, than those of case-matched controls without AR. Decreased LV systolic function, elevated serum creatinine >2 mg/dL, and intermediate- to high-risk noncardiac surgery were predictors of higher risk of cardiopulmonary complications and death.⁸ Avoid bradycardia when AR is present because of the increase in total diastolic time. These patients are monitored with invasive systemic arterial and venous catheters and/or TEE and are admitted postoperatively to an intensive monitoring setting.

16. EVIDENCE GAPS AND FUTURE DIRECTIONS

Many recommendations for the evaluation and management of VHD continue to be based on clinical experience and observational studies, with prospective RCTs limited mostly to new devices. We recommend that research on valve disease span the spectrum from basic science to prospective randomized trials, including medical therapy, and that studies focus on each stage of the disease process, from the patient at risk to the patient with end-stage disease. Newer approaches, such as artificial intelligence and machine learning, as well as imaging and engineering advances, may provide sophisticated tools for diagnosis and therapeutics. Research should be patient centered, with patients included at every stage of the research process to ensure that questions and outcomes important to patients are included in the study design, implementation, and reporting.

16.1. Prevention of Valve Disease: Stage A

On a worldwide basis, rheumatic fever remains the primary cause of VHD; global health systems outcomes studies are needed to identify impediments to successful primary and secondary prevention of rheumatic heart disease. Other approaches to prevention, such as vaccine development, and delaying disease progression once valve damage is present should also be explored. Disease prevention in patients at risk of other types of valve disease is needed, including the control of known cardiovascular risk factors. Some subgroups at risk of calcific AS can be identified, such as those with a congenital BAV or elevated lipoprotein(a) levels. However, there are no known therapies to prevent valve dysfunction in these patients. Basic science studies on the genetic and pathobiological causes of valve dysfunction will provide insight into mechanisms of disease that might allow identification of patients at risk and allow early intervention to prevent disease initiation.^{1–12}

16.2. Medical Therapy to Treat or Prevent Disease Progression: Stage B

In patients with early VHD, including those with calcific or myxomatous disease, there are currently no therapies to prevent disease progression in the valve leaflets. Instead, current recommendations are directed toward patient monitoring, with the intent to intervene once severe disease is present that results in symptoms or abnormal cardiovascular function. Basic science studies are needed to identify potential targets for prevention of progressive VHD. Focused translational studies using sensitive, advanced imaging markers of disease progression may allow more rapid clinical implementation and better design of RCTs for promising new therapies. There also has been little consideration of the interaction of valvular, ventricular, and vascular involvement in the disease process. Additional studies are needed on therapies that might prevent the adverse consequences of VHD, such as LV dysfunction and pulmonary hypertension. Most importantly, patient education and empowering patients to be active participants in managing their health conditions and participating in shared decision-making are essential.^{1–5}

16.3. Optimal Timing of Intervention: Stage C

Current approaches to identifying the optimal timing of intervention in patients with progressive valve disease are suboptimal. Symptom onset is a subjective measure and may occur too late in the disease course for optimal long-term outcomes. Despite the availability of sophisticated approaches for measurement of LV volumes, systolic function, diastolic function, and other measures of myocardial performance, recommendations continue to rely on simple linear dimensions used in published series, with data that may not reflect contemporary clinical outcomes. Studies are urgently needed that evaluate the value of newer measures of LV size, function, and myocardial structure in predicting outcomes after valve intervention, especially in patients with chronic severe AR. However, LV enlargement and dysfunction are late consequences of valve dysfunction; as more durable approaches to restoring normal valve function are developed, the benefit–risk balance for intervention will shift to earlier in the disease. Studies examining the role of earlier markers of myocardial dysfunction, such as strain and strain-rate imaging, diastolic dysfunction, circulating blood markers, and other novel approaches to defining the optimal timing of intervention, also are needed.

Few studies have included adequate numbers of older adults to make specific recommendations for this group of patients, for whom particular concerns, such

as cognitive function, frailty, and mobility challenges, may change the decision algorithms. In addition, women and minorities often are underrepresented in clinical trials. Directed efforts are needed to ensure all patient groups are included with numbers adequate to perform separate data analysis.

Given the relatively low risk associated with intervention in otherwise healthy patients and the improved options for valve repair or replacement, RCTs of intervention for severe asymptomatic VHD will be important and are in progress for some conditions, such as severe AS. Other specific conditions where clinical equipoise exists are asymptomatic severe AR with normal LV systolic function, severe primary MR with normal LV function and a high likelihood of valve repair, and the role of intervention for TR. Data from large, carefully designed registries are also needed for defining and improving quality of care. Long-term follow-up will be needed to ensure the lifetime risks of a prosthetic valve or valve repair are balanced against any benefits attributable to earlier intervention.^{1–4}

16.4. Better Options for Intervention: Stage D

Better options are needed for valve repair and replacement. The timing of intervention is based on the balance between outcomes with native valve disease and the risk and long-term durability of the valve after intervention. As valve repair and replacement options improve, the balance will shift toward earlier intervention. A valve substitute is needed that can be safely and reliably implanted, is nonthrombogenic, has hemodynamics similar to a normal native valve, and is durable. Transcatheter valve procedures offer the promise of safe implantation and excellent hemodynamics, but long-term durability beyond 5 years is not yet known. In patients who require mechanical valve replacement, oral therapy is needed that provides effective anticoagulation with a low risk of complications and no negative impact on quality of life.

Moderate to severe VHD is present in 2.5% of the US population and increases in prevalence with age. The disease affects between 4% and 9% of those 65 to 75 years of age and 12% to 13% of those >75 years of age. Many of these patients require surgical or interventional procedures. However, even with intervention, overall survival is lower than expected, and the risk of adverse outcomes attributable to VHD is high, because of both limited options for restoring normal valve function and failure to intervene at the optimal time point in the disease course. Research is urgently needed on almost every aspect of VHD to ensure that patients who already have VHD receive optimal therapy and to prevent VHD in those at risk. Approaches to improving outcomes in patients with VHD include 1)

Table 26. Evidence Gaps and Future Directions for Patients With VHD

Evidence Gaps	Future Directions
Identification of patients at risk and valve disease prevention (Stage A)	
Disease mechanisms	Basic science to identify specific targets for medical therapy
Rheumatic heart disease	Primary and secondary prevention
Calcific valve disease	Identification of patients at risk Risk factor intervention Prevention of disease initiation
Medical therapy for progressive valve disease (Stage B)	
Disease mechanisms	Basic science to identify specific targets to slow or reverse disease progression
Medical intervention	Targeted therapy using advanced imaging endpoints to study disease mechanisms
Ventricular and vascular interactions	Dynamic interplay between valve disease severity and changes in ventricular anatomy and function Modulation of ventricular and vascular dysfunction in patients with VHD
Optimal timing of intervention (Stage C)	
Improved measures of disease severity	Validation of newer measures of LV size (eg, volumes instead of dimension) and function (eg, strain) for timing of intervention decisions. Evaluation of nonimaging parameters (serum markers and other novel approaches)
Timing of intervention	Timing of intervention in asymptomatic patients with valve regurgitation Intervention for asymptomatic severe AS Intervention for moderate AS with LV dysfunction Identification of patients with secondary MR who benefit from intervention
Patient-centered research	Involvement of patients in identifying research questions, study design, and definition of outcomes
Inclusion of diverse patient groups	Adequate representation of diverse patient populations in RCTs for VHD
Decision aids	Development and validation of improved decision aids for shared decision-making with patients Implementation and validation of decision algorithms for physicians and Heart Valve Teams
Intervention options and long-term management (Stage D)	
Improved prosthetic valves	Durability of TAVI valves Nonthrombogenic durable surgical and transcatheter valves
Optimal antithrombotic therapy	Alternatives to VKA anticoagulation for mechanical valves Management of anticoagulation during pregnancy Optimal antithrombotic therapy after TAVI
Medical therapy after AVR	Medical therapy to address ventricular and vascular function Optimal blood pressure targets after valve intervention
Lower procedural risk	Approaches to lower surgical morbidity and mortality rates Prevention of postoperative AF Noninvasive approaches for correction of valve dysfunction
Prevention of complications	Approaches to avoid need for permanent pacing after SAVR or TAVI Better prevention, diagnosis and treatment of endocarditis. Better prevention of thromboembolic events.
Promoting equity	Identify and address disparities in outcomes and survival across diverse patient populations Develop novel, cost-effective approaches for long-term management in rural settings Expand access to therapies for valvular dysfunction

AF indicates atrial fibrillation; AS, aortic stenosis; AVR, aortic valve replacement; LV, left ventricular; MR, mitral regurgitation; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease; and VKA, vitamin K antagonist.

national and international registries and RCTs, 2) continuous evaluation of outcomes data at each Comprehensive and Primary Heart Valve Center, and 3) focus on patient-centric care, with involvement of the patient

in the decision-making process (Table 26). More accessible quality and outcome data are also needed from Comprehensive Valve Centers to assist cardiologists and patients to make well-informed choices.^{1–3}

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REFERENCES

Preamble

1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (US). Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (US). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: National Academies Press; 2011.
3. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–45.
4. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Available at: https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf. Accessed August 19, 2020.
5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;133:1426–8.
6. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. *Circulation*. 2014;130:1662–7.
7. Levine GN, O'Gara PT, Beckman JA, et al. Recent innovations, modifications, and evolution of ACC/AHA clinical practice guidelines: an update for our constituencies: a report of the American College of Cardiology/

American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e879–86.

1.4. Scope of the Guideline

- Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Circulation. 2006;114:e84–231.
- Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:e521–643.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–95.
- Hiratzka LF, Creager MA, Isselbacher EM, et al. Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;133:680–6.
- Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30:303–71.
- Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11:307–32.
- Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e257–354.
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199–267.
- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Developed in collaboration with the Society of Thoracic Surgeons. Circulation. 2019;140:e125–51.
- Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e698–800.
- Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr. 2009;10:1–25.
- Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017;30:372–92.
- Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2019;32:431–75.
- Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. Developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2009;22:975–1014.
- Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e783–831.
- Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020: In press.
- Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97.
- Regitz-Zagrosek V, Roos-Hesslink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39:3165–241.
- Whitlock RP, Sun JC, Fresco SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e576S–600S.
- Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33:2451–96.
- Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–91.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–61.

1.5. Class of Recommendation and Level of Evidence

- ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Available at: https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf. Accessed August 19, 2020.

2. GENERAL PRINCIPLES

2.3. Diagnosis and Follow-Up

2.3.1. Diagnostic Testing: Initial Diagnosis

- Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr. 2009;10:1–25.
- Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30:303–71.
- Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11:307–32.
- Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017;30:372–92.
- Medvedofsky D, Maffessanti F, Weinert L, et al. 2D and 3D echocardiography-derived indices of left ventricular function and shape: relationship with mortality. JACC Cardiovasc Imaging. 2018;11:1569–79.

- Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15:167–84.
- Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation*. 1985;71:1162–9.
- Thaden JJ, Tsang MY, Ayoub C, et al. Association between echocardiography laboratory accreditation and the quality of imaging and reporting for valvular heart disease. *Circ Cardiovasc Imaging*. 2017;10:e006140.

2.3.2. Diagnostic Testing: Changing Signs or Symptoms

- Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med*. 1997;337:32–41.
- Enriquez-Sarano M, Basmadjian AJ, Rossi A, et al. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. *J Am Coll Cardiol*. 1999;34:1137–44.
- Gaasch WH, John RM, Aurigemma GP. Managing asymptomatic patients with chronic mitral regurgitation. *Chest*. 1995;108:842–7.
- Lancellotti P, Rosenhek R, Pibarot P, et al. ESC Working Group on Valvular Heart Disease position paper—heart valve clinics: organization, structure, and experiences. *Eur Heart J*. 2013;34:1597–606.
- Otto CM. Timing of aortic valve surgery. *Heart*. 2000;84:211–8.
- Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1989;13:545–50.
- Rosenhek R, Rader F, Kloor U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238–44.

2.3.3. Diagnostic Testing: Routine Follow-Up

- Bonow RO, Lakatos E, Maron BJ, et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*. 1991;84:1625–35.
- Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med*. 1997;337:32–41.
- Enriquez-Sarano M, Basmadjian AJ, Rossi A, et al. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. *J Am Coll Cardiol*. 1999;34:1137–44.
- Gaasch WH, John RM, Aurigemma GP. Managing asymptomatic patients with chronic mitral regurgitation. *Chest*. 1995;108:842–7.
- Lancellotti P, Rosenhek R, Pibarot P, et al. ESC Working Group on Valvular Heart Disease position paper—heart valve clinics: organization, structure, and experiences. *Eur Heart J*. 2013;34:1597–606.
- Otto CM. Timing of aortic valve surgery. *Heart*. 2000;84:211–8.
- Rosenhek R, Rader F, Kloor U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238–44.
- Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. *J Am Coll Cardiol*. 1994;24:1536–43.
- Otto CM, Salerno CT. Timing of surgery in asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:928–9.
- Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–5.
- Rosenhek R, Lung B, Tornos P, et al. ESC Working Group on Valvular Heart Disease position paper: assessing the risk of interventions in patients with valvular heart disease. *Eur Heart J*. 2012;33:822–8, 8a, 8b.
- Taniguchi T, Morimoto T, Shiomi H, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–38.
- Kang D-H, Park S-J, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation*. 2010;121:1502–9.
- Genereux P, Stone GW, O’Gara PT, et al. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2016;67:2263–88.

2.3.4. Diagnostic Testing: Cardiac Catheterization

- Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation*. 2012;125:2138–50.

- Nishimura RA, Grantham JA, Connolly HM, et al. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106:809–13.

2.3.5. Diagnostic Testing: Exercise Testing

- Aviles RJ, Nishimura RA, Pellikka PA, et al. Utility of stress Doppler echocardiography in patients undergoing percutaneous mitral balloon valvotomy. *J Am Soc Echocardiogr*. 2001;14:676–81.
- Messika-Zeitoun D, Johnson BD, Nkomo V, et al. Cardiopulmonary exercise testing determination of functional capacity in mitral regurgitation: physiologic and outcome implications. *J Am Coll Cardiol*. 2006;47:2521–7.
- Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112:1377–82.
- Maréchaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 2010;31:1390–7.
- Otto CM, Pearlman AS, Kraft CD, et al. Physiologic changes with maximal exercise in asymptomatic valvular aortic stenosis assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1992;20:1160–7.
- Pierard LA, Lancellotti P. Stress testing in valve disease. *Heart*. 2007;93:766–72.
- Magne J, Mahjoub H, Dulgheru R, et al. Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. *Eur Heart J*. 2014;35:1608–16.
- Donal E, Masclé S, Brunet A, et al. Prediction of left ventricular ejection fraction 6 months after surgical correction of organic mitral regurgitation: the value of exercise echocardiography and deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2012;13:922–30.
- Wahi S, Haluska B, Pasquet A, et al. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. *Heart*. 2000;84:606–14.
- Gentry JL 3rd, Parikh PK, Alashi A, et al. Characteristics and outcomes in a contemporary group of patients with suspected significant mitral stenosis undergoing treadmill stress echocardiography. *Circ Cardiovasc Imaging*. 2019;12:e009062.
- Lancellotti P, Dulgheru R, Go YY, et al. Stress echocardiography in patients with native valvular heart disease. *Heart*. 2018;104:807–13.

2.4. Basic Principles of Medical Therapy

- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–61.
- Gati S, Malhotra A, Sharma S. Exercise recommendations in patients with valvular heart disease. *Heart*. 2019;105:106–10.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–646.

2.4.1. Secondary Prevention of Rheumatic Fever

- Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation*. 2009;119:1541–51.

2.4.2. IE Prophylaxis

- Glenny A-M, Oliver R, Roberts GJ, et al. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database Syst Rev*. 2013;CD003813.
- Mougeot FKB, Saunders SE, Brennan MT, et al. Associations between bacteremia from oral sources and distant-site infections: tooth brushing versus single tooth extraction. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;119:430–5.

3. Sherman-Weber S, Axelrod P, Suh B, et al. Infective endocarditis following orthotopic heart transplantation: 10 cases and a review of the literature. *Transpl Infect Dis*. 2004;6:165–70.
4. Lockhart PB, Brennan MT, Sasser HC, et al. Bacteremia associated with toothbrushing and dental extraction. *Circulation*. 2008;117:3118–25.
5. Geist S-MRY, Fitzpatrick S, Geist JR. American Heart Association 2007 guidelines on prevention of infective endocarditis. *J Mich Dent Assoc*. 2007;89:50–6.
6. Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clin Infect Dis*. 2006;42:e102–7.
7. The 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;36:3036–7.
8. Horstkotte D, Rosin H, Friedrichs W, et al. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. *Eur Heart J*. 1987;8:379–81.
9. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Ann Intern Med*. 1998;129:761–9.
10. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation*. 1997;96:358–66.
11. Guarner-Argente C, Shah P, Buchner A, et al. Use of antimicrobials for EUS-guided FNA of pancreatic cysts: a retrospective, comparative analysis. *Gastrointest Endosc*. 2011;74:81–6.
12. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–54.
13. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2015;36:3036–7.
14. Prophylaxis Against Infective Endocarditis: Antimicrobial Prophylaxis Against Infective Endocarditis in Adults and Children Undergoing Interventional Procedures. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK554353/>. Accessed October 12, 2020.
15. Thornhill MH, Gibson TB, Cutler E, et al. Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. *J Am Coll Cardiol*. 2018;72:2443–54.
16. Desimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. *Circulation*. 2012;126:60–4.
17. Dayer MJ, Jones S, Prendergast B, et al. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. *Lancet*. 2015;385:1219–28.
18. Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol*. 2012;59:1968–76.
19. Pasquali SK, He X, Mohamad Z, et al. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J*. 2012;163:894–9.
20. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65:2070–6.
21. Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ*. 2011;342:d2392.
22. Strom BL, Abrutyn E, Berlin JA, et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation*. 2000;102:2842–8.
23. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. *Circulation*. 2015;131:1566–74.
24. Mangner N, Woitek F, Haussig S, et al. Incidence, predictors, and outcome of patients developing infective endocarditis following transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2907–8.
25. Karavas AN, Filsoofi F, Mihajlovic T, et al. Risk factors and management of endocarditis after mitral valve repair. *J Heart Valve Dis*. 2002;11:660–4.
26. Gillinov AM, Faber CN, Sabik JF, et al. Endocarditis after mitral valve repair. *Ann Thorac Surg*. 2002;73:1813–6.
27. Botoman VA, Surawicz CM. Bacteremia with gastrointestinal endoscopic procedures. *Gastrointest Endosc*. 1986;32:342–6.
28. Low DE, Shoenut JP, Kennedy JK, et al. Risk of bacteremia with endoscopic sphincterotomy. *Can J Surg*. 1987;30:421–3.
29. Low DE, Shoenut JP, Kennedy JK, et al. Prospective assessment of risk of bacteremia with colonoscopy and polypectomy. *Dig Dis Sci*. 1987;32:1239–43.
30. Wolf JS, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol*. 2008;179:1379–90.

2.4.3. Anticoagulation for AF in Patients With VHD

1. Pan K-L, Singer DE, Ovbiagele B, et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005835.
2. Lip GYH, Jensen M, Melgaard L, et al. Stroke and bleeding risk scores in patients with atrial fibrillation and valvular heart disease: evaluating “valvular heart disease” in a nationwide cohort study. *Europace*. 2019;21:33–40.
3. Vora AN, Dai D, Matsuoka R, et al. Incidence, management, and associated clinical outcomes of new-onset atrial fibrillation following transcatheter aortic valve replacement: an analysis from the STS/ACC TVT registry. *JACC Cardiovasc Interv*. 2018;11:1746–56.
4. Seeger J, Gonska B, Rodewald C, et al. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:66–74.
5. Jochheim D, Barbanti M, Capretti G, et al. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2019;12:1566–76.
6. Mangner N, Crusius L, Haussig S, et al. Continued versus interrupted oral anticoagulation during transfemoral transcatheter aortic valve implantation and impact of postoperative anticoagulant management on outcome in patients with atrial fibrillation. *Am J Cardiol*. 2019;123:1134–41.
7. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–14.
8. De Caterina R, Renda G, Carnicelli AP, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2017;69:1372–82.
9. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. 2017;135:1273–5.
10. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2015;132:624–32.
11. Guimarães PO, Pokorney SD, Lopes RD, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: insights from the ARISTOTLE trial. *Clin Cardiol*. 2019;42:568–71.
12. Vinereanu D, Wang A, Mulder H, et al. Outcomes in anticoagulated patients with atrial fibrillation and with mitral or aortic valve disease. *Heart*. 2018;104:1292–9.
13. Breithardt G, Baumgartner H, Berkowitz SD, et al. Native valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. *Heart*. 2016;102:1036–43.
14. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J*. 2014;35:3377–85.
15. Siontis KC, Yao X, Gersh BJ, et al. Direct oral anticoagulants in patients with atrial fibrillation and valvular heart disease other than significant mitral stenosis and mechanical valves: a meta-analysis. *Circulation*. 2017;135:714–6.
16. Andrade JG, Meseguer E, Didier R, et al. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with bioprosthetic valves. *Expert Rev Cardiovasc Ther*. 2018;1–6.
17. Renda G, Ricci F, Giugliano RP, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol*. 2017;69:1363–71.
18. Briasoulis A, Inampudi C, Akintoye E, et al. Safety and efficacy of novel oral anticoagulants versus warfarin in Medicare beneficiaries with atrial fibrillation and valvular heart disease. *J Am Heart Assoc*. 2018;7:e008773.

19. Philippart R, Brunet-Bernard A, Clementy N, et al. Oral anticoagulation, stroke and thromboembolism in patients with atrial fibrillation and valve bioprosthesis. The Loire Valley Atrial Fibrillation Project. *Thromb Haemost*. 2016;115:1056–63.
20. Duraes AR, de Souza Roriz P, de Almeida Nunes B, et al. Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively: DAWA Pilot Study. *Drugs R D*. 2016;16:149–54.
21. Noseworthy PA, Yao X, Shah ND, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease. *Int J Cardiol*. 2016;209:181–3.
22. Kim JY, Kim S-H, Myong J-P, et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol*. 2019;73:1123–31.
23. Dangas GD, Tijssen JGP, Wohrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:120–9.

2.5. Evaluation of Surgical and Interventional Risk

1. Edwards FH, Cohen DJ, O'Brien SM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. *JAMA Cardiol*. 2016;1:46–52.
2. Pilgrim T, Franzone A, Stortecky S, et al. Predicting mortality after transcatheter aortic valve replacement: external validation of the Transcatheter Valve Therapy registry model. *Circ Cardiovasc Interv*. 2017;10:e005481.
3. Greason KL, Eleid MF, Nkomo VT, et al. Predictors of 1-year mortality after transcatheter aortic valve replacement. *J Card Surg*. 2018;33:243–9.
4. Arsalan M, Weferling M, Hecker F, et al. TAVI risk scoring using established versus new scoring systems: role of the new STS/ACC model. *EuroIntervention*. 2018;13:1520–6.
5. Kiani S, Kamioka N, Black GB, et al. Development of a risk score to predict new pacemaker implantation after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2019;12:2133–42.
6. Thourani VH, O'Brien SM, Kelly JJ, et al. Development and application of a risk prediction model for in-hospital stroke after transcatheter aortic valve replacement: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Ann Thorac Surg*. 2019;107:1097–103.
7. Lytwyn J, Stammers AN, Kehler DS, et al. The impact of frailty on functional survival in patients 1 year after cardiac surgery. *J Thorac Cardiovasc Surg*. 2017;154:1990–9.
8. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014;63:747–62.
9. Schoenenberger AW, Moser A, Bertschi D, et al. Improvement of risk prediction after transcatheter aortic valve replacement by combining frailty with conventional risk scores. *JACC Cardiovasc Interv*. 2018;11:395–403.
10. Afilalo J, Lauck S, Kim DH, et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol*. 2017;70:689–700.
11. Arnold SV, O'Brien SM, Vemulapalli S, et al. Inclusion of functional status measures in the risk adjustment of 30-day mortality after transcatheter aortic valve replacement: a report from the Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC Cardiovasc Interv*. 2018;11:581–9.
12. Arnold SV, Reynolds MR, Lei Y, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation*. 2014;129:2682–90.
13. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012;366:1696–704.
14. Suri RM, Gulack BC, Brennan JM, et al. Outcomes of patients with severe chronic lung disease who are undergoing transcatheter aortic valve replacement. *Ann Thorac Surg*. 2015;100:2136–45.
15. Thourani VH, Forcillo J, Beohar N, et al. Impact of preoperative chronic kidney disease in 2,531 high-risk and inoperable patients undergoing transcatheter aortic valve replacement in the PARTNER Trial. *Ann Thorac Surg*. 2016;102:1172–80.
16. Puri R, Jung B, Cohen DJ, et al. TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J*. 2016;37:2217–25.
17. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol*. 2014;64:172–81.
18. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. *J Am Coll Cardiol*. 2014;64:182–92.
19. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–18.
20. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346:1128–37.
21. Vemulapalli S, Carroll JD, Mack MJ, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. *N Engl J Med*. 2019;380:2541–50.
22. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT registry. *J Am Coll Cardiol*. 2017;70:29–41.
23. Russo MJ, McCabe JM, Thourani VH, et al. Case volume and outcomes after TAVR with balloon-expandable prostheses: insights from TVT registry. *J Am Coll Cardiol*. 2019;73:427–40.
24. Bolling SF, Li S, O'Brien SM, et al. Predictors of mitral valve repair: clinical and surgeon factors. *Ann Thorac Surg*. 2010;90:1904–11.
25. Badhwar V, Offenloch JC, Rovin JD, et al. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg*. 2012;93:748–53.
26. Hart SA, Krasuski RA, Wang A, et al. Pulmonary hypertension and elevated transpulmonary gradient in patients with mitral stenosis. *J Heart Valve Dis*. 2010;19:708–15.
27. Weiner MM, Hofer I, Lin H-M, et al. Relationship among surgical volume, repair quality, and perioperative outcomes for repair of mitral insufficiency in a mitral valve reference center. *J Thorac Cardiovasc Surg*. 2014;148:2021–6.
28. LaPar DJ, Ailawadi G, Isbell JM, et al. Mitral valve repair rates correlate with surgeon and institutional experience. *J Thorac Cardiovasc Surg*. 2014;148:995–1003.
29. Kilic A, Shah AS, Conte JV, et al. Operative outcomes in mitral valve surgery: combined effect of surgeon and hospital volume in a population-based analysis. *J Thorac Cardiovasc Surg*. 2013;146:638–46.
30. Gammie JS, O'Brien SM, Griffith BP, et al. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation*. 2007;115:881–7.
31. Vassileva CM, McNeely C, Spertus J, et al. Hospital volume, mitral repair rates, and mortality in mitral valve surgery in the elderly: an analysis of US hospitals treating Medicare fee-for-service patients. *J Thorac Cardiovasc Surg*. 2015;149:762–8, e1.
32. Chikwe J, Toyoda N, Anyanwu AC, et al. Relation of mitral valve surgery volume to repair rate, durability, and survival. *J Am Coll Cardiol*. 2017;69:2397–406.
33. Chhatrivala AK, Vemulapalli S, Holmes DR Jr, et al. Institutional experience with transcatheter mitral valve repair and clinical outcomes: insights from the TVT registry. *JACC Cardiovasc Interv*. 2019;12:1342–52.
34. Katz S, Downs TD, Cash HR, et al. Progress in development of the index of ADL. *Gerontologist*. 1970;10:20–30.
35. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489–95.

2.6. The Multidisciplinary Heart Valve Team and Heart Valve Centers

1. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. *N Engl J Med*. 2003;349:2117–27.
2. Patel HJ, Herbert MA, Drake DH, et al. Aortic valve replacement: using a statewide cardiac surgical database identifies a procedural volume hinge point. *Ann Thorac Surg*. 2013;96:1560–5.
3. Dewey TM, Herbert MA, Ryan WH, et al. Influence of surgeon volume on outcomes with aortic valve replacement. *Ann Thorac Surg*. 2012;93:1107–12.
4. McNeely C, Markwell S, Filson K, et al. Effect of hospital volume on prosthesis use and mortality in aortic valve operations in the elderly. *Ann Thorac Surg*. 2016;101:585–90.
5. Khara R, Pandey A, Koshy T, et al. Role of hospital volumes in identifying low-performing and high-performing aortic and aortic valve surgical centers in the United States. *JAMA Cardiol*. 2017;2:1322–31.
6. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT registry. *J Am Coll Cardiol*. 2017;70:29–41.

7. Bolling SF, Li S, O'Brien SM, et al. Predictors of mitral valve repair: clinical and surgeon factors. *Ann Thorac Surg*. 2010;90:1904–11.
8. Chikwe J, Toyoda N, Anyanwu AC, et al. Relation of mitral valve surgery volume to repair rate, durability, and survival. *J Am Coll Cardiol*. 2017;69:2397–406.
9. Gammie JS, O'Brien SM, Griffith BP, et al. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation*. 2007;115:881–7.
10. Kilic A, Shah AS, Conte JV, et al. Operative outcomes in mitral valve surgery: combined effect of surgeon and hospital volume in a population-based analysis. *J Thorac Cardiovasc Surg*. 2013;146:638–46.
11. Vassileva CM, Boley T, Markwell S, et al. Impact of hospital annual mitral procedural volume on mitral valve repair rates and mortality. *J Heart Valve Dis*. 2012;21:41–7.
12. Nishimura RA, O'Gara PT, Bavaria JE, et al. 2019 AATS/ACC/AASE/SCAI/STS expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2019;73:2609–35.
13. Ando T, Adegala O, Villablanca PA, et al. Failure to rescue, hospital volume, and in-hospital mortality after transcatheter aortic valve implantation. *Am J Cardiol*. 2018;122:828–32.
14. Edwards FH, Ferraris VA, Kurlansky PA, et al. Failure to rescue rates after coronary artery bypass grafting: an analysis from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg*. 2016;102:458–64.
15. Scali ST, Giles KA, Kubilis P, et al. Impact of hospital volume on patient safety indicators and failure to rescue following open aortic aneurysm repair. *J Vasc Surg*. 2020;71:1135–46.e4.
16. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. *Med Care*. 2011;49:1076–81.
17. Gonzalez AA, Dimick JB, Birkmeyer JD, et al. Understanding the volume-outcome effect in cardiovascular surgery: the role of failure to rescue. *JAMA Surg*. 2014;149:119–23.
18. Ward ST, Dimick JB, Zhang W, et al. Association between hospital staffing models and failure to rescue. *Ann Surg*. 2019;270:91–4.
19. Wakeam E, Asafu-Adjiei D, Ashley SW, et al. The association of intensivists with failure-to-rescue rates in outlier hospitals: results of a national survey of intensive care unit organizational characteristics. *J Crit Care*. 2014;29:930–5.
20. Holmes DR, Rich JB, Zoghbi WA, et al. The heart team of cardiovascular care. *J Am Coll Cardiol*. 2013;61:903–7.
21. Kadem L, Dumesnil JG, Rieu R, et al. Impact of systemic hypertension on the assessment of aortic stenosis. *Heart*. 2005;91:354–61.
22. Laskey WK, Kussmaul WG 3rd. Hypertension, aortic valve stenosis, and the aorta: more lessons from TAVR. *J Am Coll Cardiol*. 2015;65:434–6.
23. Yotti R, Bermejo J, Gutiérrez-Ibañes E, et al. Systemic vascular load in calcific degenerative aortic valve stenosis: insight from percutaneous valve replacement. *J Am Coll Cardiol*. 2015;65:423–33.
24. Lindman BR, Otto CM. Time to treat hypertension in patients with aortic stenosis. *Circulation*. 2013;128:1281–3.
25. Lin SS, Roger VL, Pascoe R, et al. Dobutamine stress Doppler hemodynamics in patients with aortic stenosis: feasibility, safety, and surgical correlations. *Am Heart J*. 1998;136:1010–6.
26. Monin JL, Monchi M, Gest V, et al. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. *J Am Coll Cardiol*. 2001;37:2101–7.
27. Clavel M-A, Fuchs C, Burwash IG, et al. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS Study. *Circulation*. 2008;118:S234–42.
28. Otto CM, Pearlman AS, Comess KA, et al. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol*. 1986;7:509–17.
29. Oh JK, Taliereio CP, Holmes DR, et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol*. 1988;11:1227–34.
30. Jander N, Hochholzer W, Kaufmann BA, et al. Velocity ratio predicts outcomes in patients with low gradient severe aortic stenosis and preserved EF. *Heart*. 2014;100:1946–53.
31. Pawade T, Clavel M-A, Tribouilloy C, et al. Computed tomography aortic valve calcium scoring in patients with aortic stenosis. *Circ Cardiovasc Imaging*. 2018;11:e007146.
32. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–7.
33. Messika-Zeitoun D, Aubry M-C, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. *Circulation*. 2004;110:356–62.
34. Cuffe C, Serfaty J-M, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart*. 2011;97:721–6.
35. Clavel M-A, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol*. 2014;64:1202–13.
36. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.
37. Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation*. 1985;71:1162–9.
38. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–70.
39. Zoghbi WA, Farmer KL, Soto JG, et al. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation*. 1986;73:452–9.
40. Otto CM, Pearlman AS. Doppler echocardiography in adults with symptomatic aortic stenosis. Diagnostic utility and cost-effectiveness. *Arch Intern Med*. 1988;148:2553–60.
41. Rosenhek R, Klear U, Schemper M, et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199–205.
42. Otto CM. Valvular stenosis. In: Otto CM, ed. *The Textbook of Clinical Echocardiography*. 6th ed. Philadelphia, PA: Elsevier; 2018:288–323.
43. Stewart RAH, Kerr AJ, Whalley GA, et al. Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis. *Eur Heart J*. 2010;31:2216–22.
44. Jander N, Minners J. Aortic stenosis: disease severity, progression, and timing and type of intervention. In: Otto CM, ed. *The Practice of Clinical Echocardiography*. 6th ed. Philadelphia, PA: Elsevier; 2021. In press.
45. Nishimura RA, Grantham JA, Connolly HM, et al. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic

2.7. Management of Patients With VHD After Valve Intervention

2.7.4. Periodic Imaging After Valve Intervention

1. Salaun E, Mahjoub H, Girerd N, et al. Rate, timing, correlates, and outcomes of hemodynamic valve deterioration after bioprosthetic surgical aortic valve replacement. *Circulation*. 2018;138:971–85.
2. Salaun E, Mahjoub H, Dahou A, et al. Hemodynamic deterioration of surgically implanted bioprosthetic aortic valves. *J Am Coll Cardiol*. 2018;72:241–51.

3. AORTIC STENOSIS

3.2.1. Diagnosis and Follow-Up

3.2.1.1. Diagnostic Testing: Initial Diagnosis

1. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–92.
2. Gardezi SKM, Myerson SG, Chambers J, et al. Cardiac auscultation poorly predicts the presence of valvular heart disease in asymptomatic primary care patients. *Heart*. 2018;104:1832–5.
3. Eleid MF, Michelena HI, Nkomo VT, et al. Causes of death and predictors of survival after aortic valve replacement in low flow vs. normal flow severe aortic stenosis with preserved ejection fraction. *Eur Heart J Cardiovasc Imaging*. 2015;16:1270–5.

function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106:809–13.

29. Clavel MA, Webb JG, Rodés-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation*. 2010;122:1928–36.
30. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–4.
31. Blais C, Burwash IG, Mundigler G, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. *Circulation*. 2006;113:711–21.
32. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1845–53.
33. Bradley SM, Foag K, Monteagudo K, et al. Use of routinely captured echocardiographic data in the diagnosis of severe aortic stenosis. *Heart*. 2019;105:112–6.

3.2.1.3. Diagnostic Testing: Routine Follow-Up

1. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1989;13:545–50.
2. Brenner SJ, Duffy CI, Thomas JD, et al. Progression of aortic stenosis in 394 patients: relation to changes in myocardial and mitral valve dysfunction. *J Am Coll Cardiol*. 1995;25:305–10.
3. Roger VL, Tajik AJ, Bailey KR, et al. Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. *Am Heart J*. 1990;119:331–8.
4. Bahler RC, Desser DR, Finkelhor RS, et al. Factors leading to progression of valvular aortic stenosis. *Am J Cardiol*. 1999;84:1044–8.
5. Palta S, Pai AM, Gill KS, et al. New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation*. 2000;101:2497–502.
6. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–7.
7. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–56.
8. Cosmi JE, Kort S, Tunick PA, et al. The risk of the development of aortic stenosis in patients with “benign” aortic valve thickening. *Arch Intern Med*. 2002;162:2345–7.
9. Novaro GM, Katz R, Aviles RJ, et al. Clinical factors, but not C-reactive protein, predict progression of calcific aortic-valve disease: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2007;50:1992–8.
10. Owens DS, Katz R, Takasu J, et al. Incidence and progression of aortic valve calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Cardiol*. 2010;105:701–8.
11. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. *JAMA*. 2008;300:1317–25.
12. Michelena HI, Desjardins VA, Avierinos J-F, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*. 2008;117:2776–84.
13. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. *Circ Res*. 2013;113:223–37.

3.2.1.4. Diagnostic Testing: Cardiac Catheterization

1. Shavelle DM. Evaluation of valvular heart disease by cardiac catheterization and angiography. In: Otto CM, Bonow RO, eds. *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*. 4th ed. Philadelphia, PA: Elsevier/Saunders; 2014:91–106.
2. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation*. 2012;125:2138–50.

3.2.1.5. Diagnostic Testing: Exercise Testing

1. Saeed S, Rajani R, Seifert R, et al. Exercise testing in patients with asymptomatic moderate or severe aortic stenosis. *Heart*. 2018;104:1836–42.
2. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–13.

3. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–70.
4. Maréchaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 2010;31:1390–7.
5. Atterhög JH, Jonsson B, Samuelsson R. Exercise testing: a prospective study of complication rates. *Am Heart J*. 1979;98:572–9.
6. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1989;13:545–50.
7. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112:1377–82.
8. Amato MC, Moffa PJ, Werner KE, et al. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001;86:381–6.
9. Alborino D, Hoffmann JL, Fournet PC, et al. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. *J Heart Valve Dis*. 2002;11:204–9.
10. Takeda S, Rimington H, Chambers J. Prediction of symptom-onset in aortic stenosis: a comparison of pressure drop/flow slope and haemodynamic measures at rest. *Int J Cardiol*. 2001;81:131–7.
11. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation*. 2012;126:2465–72.
12. Dhoble A, Sarano ME, Kopecky SL, et al. Safety of symptom-limited cardiopulmonary exercise testing in patients with aortic stenosis. *Am J Med*. 2012;125:704–8.

3.2.2. Medical Therapy

1. Nazarzadeh M, Pinho-Gomes A-C, Smith Byrne K, et al. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiol*. 2019;4:788–95.
2. Rahimi K, Mohseni H, Kiran A, et al. Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 million UK adults. *Eur Heart J*. 2018;39:3596–603.
3. Nielsen OW, Sajadieh A, Sabbah M, et al. Assessing optimal blood pressure in patients with asymptomatic aortic valve stenosis: the Simvastatin Ezetimibe in Aortic Stenosis study (SEAS). *Circulation*. 2016;134:455–68.
4. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–56.
5. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med*. 2005;352:2389–97.
6. Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the Aortic Stenosis Progression Observation: Measuring Effects Of Rosuvastatin (ASTRONOMER) trial. *Circulation*. 2010;121:306–14.
7. Ochiai T, Saito S, Yamanaka F, et al. Renin-angiotensin system blockade therapy after transcatheter aortic valve implantation. *Heart*. 2018;104:644–51.
8. Inohara T, Manandhar P, Kosinski AS, et al. Association of renin-angiotensin inhibitor treatment with mortality and heart failure readmission in patients with transcatheter aortic valve replacement. *JAMA*. 2018;320:2231–41.
9. O'Brien KD, Zhao X-Q, Shavelle DM, et al. Hemodynamic effects of the angiotensin-converting enzyme inhibitor, ramipril, in patients with mild to moderate aortic stenosis and preserved left ventricular function. *J Investig Med*. 2004;52:185–91.
10. Chockalingam A, Venkatesan S, Subramaniam T, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J*. 2004;147:E19.
11. Nadir MA, Wei L, Elder DHJ, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol*. 2011;58:570–6.
12. Rieck AE, Cramariuc D, Boman K, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. *Hypertension*. 2012;60:90–7.
13. Briand M, Dumesnil JG, Kadem L, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. *J Am Coll Cardiol*. 2005;46:291–8.

14. Moura LM, Ramos SF, Zamorano JL, et al. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. *J Am Coll Cardiol*. 2007;49:554–61.
15. Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease—2011 update. *Circulation*. 2011;124:1783–91.
16. Hansson NH, Sorensen J, Harms HJ, et al. Metoprolol reduces hemodynamic and metabolic overload in asymptomatic aortic valve stenosis patients: a randomized trial. *Circ Cardiovasc Imaging*. 2017;10:e006557.
17. Lindman BR, Zajarias A, Madrazo JA, et al. Effects of phosphodiesterase type 5 inhibition on systemic and pulmonary hemodynamics and ventricular function in patients with severe symptomatic aortic stenosis. *Circulation*. 2012;125:2353–62.

3.2.3. Timing of Intervention

1. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–91.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–607.
3. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012;366:1696–704.
4. Otto CM, Pearlman AS. Doppler echocardiography in adults with symptomatic aortic stenosis. Diagnostic utility and cost-effectiveness. *Arch Intern Med*. 1988;148:2553–60.
5. Turina J, Hess O, Sepulcri F, et al. Spontaneous course of aortic valve disease. *Eur Heart J*. 1987;8:471–83.
6. Kelly TA, Rothbart RM, Cooper CM, et al. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol*. 1988;61:123–30.
7. Pellikka PA, Nishimura RA, Bailey KR, et al. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol*. 1990;15:1012–7.
8. Dahl JS, Eleid MF, Michelena HI, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circ Cardiovasc Imaging*. 2015;8:e002917.
9. Taniguchi T, Morimoto T, Shiomi H, et al. Prognostic impact of left ventricular ejection fraction in patients with severe aortic stenosis. *JACC Cardiovasc Interv*. 2018;11:145–57.
10. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. *J Am Coll Cardiol*. 2018;71:1313–21.
11. Bohbot Y, de Meester de Ravenstein C, Chadha G, et al. Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. *JACC Cardiovasc Imaging*. 2019;12:38–48.
12. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–7.
13. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–70.
14. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–5.
15. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. *Heart*. 2010;96:1364–71.
16. Kang D-H, Park S-J, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation*. 2010;121:1502–9.
17. Tribouilloy C, Lévy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol*. 2009;53:1865–73.
18. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation*. 2013;127:2316–26.
19. Anjan VY, Herrmann HC, Pibarot P, et al. Evaluation of flow after transcatheter aortic valve replacement in patients with low-flow aortic stenosis: a secondary analysis of the PARTNER randomized clinical trial. *JAMA Cardiol*. 2016;1:584–92.
20. Lopez-Marco A, Miller H, Youhana A, et al. Low-flow low-gradient aortic stenosis: surgical outcomes and mid-term results after isolated aortic valve replacement. *Eur J Cardiothorac Surg*. 2016;49:1685–90.
21. O'Sullivan CJ, Englberger L, Hosek N, et al. Clinical outcomes and revascularization strategies in patients with low-flow, low-gradient severe aortic valve stenosis according to the assigned treatment modality. *JACC Cardiovasc Interv*. 2015;8:704–17.
22. Nishimura RA, Grantham JA, Connolly HM, et al. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106:809–13.
23. Monin J-L, Quéré J-P, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–24.
24. Fougères E, Tribouilloy C, Monchi M, et al. Outcomes of pseudo-severe aortic stenosis under conservative treatment. *Eur Heart J*. 2012;33:2426–33.
25. Eleid MF, Padang R, Al-Hijji M, et al. Hemodynamic response in low-flow low-gradient aortic stenosis with preserved ejection fraction after TAVR. *J Am Coll Cardiol*. 2019;73:1731–2.
26. Rusinaru D, Bohbot Y, Ringle A, et al. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *Eur Heart J*. 2018;39:1992–9.
27. Zheng Q, Djohan AH, Lim E, et al. Effects of aortic valve replacement on severe aortic stenosis and preserved systolic function: systematic review and network meta-analysis. *Sci Rep*. 2017;7:5092.
28. Maréchaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 2010;31:1390–7.
29. Saeed S, Mancica G, Rajani R, et al. Exercise treadmill testing in moderate or severe aortic stenosis: the left ventricular correlates of an exaggerated blood pressure rise. *J Am Heart Assoc*. 2018;7:e010735.
30. Saeed S, Rajani R, Seifert R, et al. Exercise testing in patients with asymptomatic moderate or severe aortic stenosis. *Heart*. 2018;104:1836–42.
31. Kang D-H, Park S-J, Lee S-A, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382:111–9.
32. Nakatsuma K, Taniguchi T, Morimoto T, et al. B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. *Heart*. 2019;105:384–90.
33. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol*. 2018;3:1060–8.
34. Taniguchi T, Morimoto T, Shiomi H, et al. Sudden death in patients with severe aortic stenosis: observations from the CURRENT AS registry. *J Am Heart Assoc*. 2018;7:e008397.
35. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation*. 2010;121:151–6.
36. Bergler-Klein J, Klaar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation*. 2004;109:2302–8.
37. Gerber IL, Stewart RAH, Legget ME, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. *Circulation*. 2003;107:1884–90.
38. Lim P, Monin JL, Monchi M, et al. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. *Eur Heart J*. 2004;25:2048–53.
39. Taniguchi T, Morimoto T, Shiomi H, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–38.
40. Nishimura S, Izumi C, Nishiga M, et al. Predictors of rapid progression and clinical outcome of asymptomatic severe aortic stenosis. *Circ J*. 2016;80:1863–9.
41. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005;111:3316–26.
42. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988;9(suppl E):57–64.
43. Kvidal P, Bergström R, Hörte LG, et al. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol*. 2000;35:747–56.

44. Murphy ES, Lawson RM, Starr A, et al. Severe aortic stenosis in patients 60 years of age or older: left ventricular function and 10-year survival after valve replacement. *Circulation*. 1981;64:1184–8.
45. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88:S23–42.
46. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. *Circulation*. 1982;66:1105–10.
47. Oh JK, Taliencio CP, Holmes DR, et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol*. 1988;11:1227–34.
48. Galan A, Zoghbi WA, Quiñones MA. Determination of severity of valvular aortic stenosis by Doppler echocardiography and relation of findings to clinical outcome and agreement with hemodynamic measurements determined at cardiac catheterization. *Am J Cardiol*. 1991;67:1007–12.
49. Rosenhek R, Klaar U, Schemper M, et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199–205.
50. Stewart RAH, Kerr AJ, Whalley GA, et al. Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis. *Eur Heart J*. 2010;31:2216–22.
51. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–56.
52. Kennedy KD, Nishimura RA, Holmes DR Jr, et al. Natural history of moderate aortic stenosis. *J Am Coll Cardiol*. 1991;17:313–9.
53. Jander N, Minners J, Holme I, et al. Outcome of patients with low-gradient “severe” aortic stenosis and preserved ejection fraction. *Circulation*. 2011;123:887–95.
54. Saito T, Muro T, Takeda H, et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. *Am J Cardiol*. 2012;110:93–7.
55. Pereira JJ, Lauer MS, Bashir M, et al. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol*. 2002;39:1356–63.
56. Clavel MA, Webb JG, Rodés-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation*. 2010;122:1928–36.
57. Connolly HM, Oh JK, Orszulak TA, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation*. 1997;95:2395–400.
58. Quéré J-P, Monin J-L, Levy F, et al. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. *Circulation*. 2006;113:1738–44.
59. Pai RG, Varadarajan P, Razzouk A. Survival benefit of aortic valve replacement in patients with severe aortic stenosis with low ejection fraction and low gradient with normal ejection fraction. *Ann Thorac Surg*. 2008;86:1781–9.
60. Levy F, Laurent M, Monin JL, et al. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol*. 2008;51:1466–72.
61. Gotzmann M, Lindstaedt M, Bojara W, et al. Clinical outcome of transcatheter aortic valve implantation in patients with low-flow, low gradient aortic stenosis. *Catheter Cardiovasc Interv*. 2012;79:693–701.
62. Pereira JJ, Balaban K, Lauer MS, et al. Aortic valve replacement in patients with mild or moderate aortic stenosis and coronary bypass surgery. *Am J Med*. 2005;118:735–42.
63. Smith WT, Ferguson TB Jr, Ryan T, et al. Should coronary artery bypass graft surgery patients with mild or moderate aortic stenosis undergo concomitant aortic valve replacement? A decision analysis approach to the surgical dilemma. *J Am Coll Cardiol*. 2004;44:1241–7.
64. Gillinov AM, Garcia MJ. When is concomitant aortic valve replacement indicated in patients with mild to moderate stenosis undergoing coronary revascularization? *Curr Cardiol Rep*. 2005;7:101–4.
65. Bhattacharyya S, Hayward C, Pepper J, et al. Risk stratification in asymptomatic severe aortic stenosis: a critical appraisal. *Eur Heart J*. 2012;33:2377–87.
66. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.
67. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–4.
68. Tarantini G, Covolo E, Razzolini R, et al. Valve replacement for severe aortic stenosis with low transvalvular gradient and left ventricular ejection fraction exceeding 0.50. *Ann Thorac Surg*. 2011;91:1808–15.
69. Clavel M-A, Dumesnil JG, Capoulade R, et al. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1259–67.
70. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol*. 2012;59:235–43.
71. Mehrotra P, Jansen K, Flynn AW, et al. Differential left ventricular remodeling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis. *Eur Heart J*. 2013;34:1906–14.
72. Lauten J, Rost C, Breithardt OA, et al. Invasive hemodynamic characteristics of low gradient severe aortic stenosis despite preserved ejection fraction. *J Am Coll Cardiol*. 2013;61:1799–808.
73. Mangner N, Stachel G, Woitek F, et al. Predictors of mortality and symptomatic outcome of patients with low-flow severe aortic stenosis undergoing transcatheter aortic valve replacement. *J Am Heart Assoc*. 2018;7:e010287.
74. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–91.
75. Ozkan A, Hachamovitch R, Kapadia SR, et al. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. *Circulation*. 2013;128:622–31.
76. Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the Aortic Stenosis Progression Observation: Measuring Effects Of Rosuvastatin (ASTRONOMER) trial. *Circulation*. 2010;121:306–14.
77. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112:1377–82.
78. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–13.
79. Alborino D, Hoffmann JL, Fournet PC, et al. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. *J Heart Valve Dis*. 2002;11:204–9.
80. Takeda S, Rimington H, Chambers J. Prediction of symptom-onset in aortic stenosis: a comparison of pressure drop/flow slope and haemodynamic measures at rest. *Int J Cardiol*. 2001;81:131–7.
81. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation*. 2012;126:2465–72.
82. Dayan V, Vignolo G, Magne J, et al. Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *J Am Coll Cardiol*. 2015;66:2594–603.

3.2.4. Choice of Intervention

3.2.4.1. Choice of Mechanical Versus Bioprosthetic AVR

1. Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med*. 2017;377:1847–57.
2. Badhwar V, Offenloch JC, Rovin JD, et al. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg*. 2012;93:748–53.
3. Brown ML, Schaff HV, Lahr BD, et al. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. *J Thorac Cardiovasc Surg*. 2008;135:878–84.
4. van Geldorp MWA, Eric Jamieson WR, Kappetein AP, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. *J Thorac Cardiovasc Surg*. 2009;137:881–6, 866.e1–5.
5. Kulik A, Bédard P, Lam B-K, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. *Eur J Cardiothorac Surg*. 2006;30:485–91.
6. Glaser N, Jackson V, Holzmann MJ, et al. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. *Eur Heart J*. 2016;37:2658–67.

7. Chikwe J, Chiang YP, Egorova NN, et al. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. *JAMA*. 2015;313:1435–42.
8. McClure RS, McGurk S, Cevasco M, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2014;148:1931–9.
9. Chiang YP, Chikwe J, Moskowitz AJ, et al. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA*. 2014;312:1323–9.
10. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. *J Thorac Cardiovasc Surg*. 2014;147:117–26.
11. Buratto E, Shi WY, Wynne R, et al. Improved survival after the Ross procedure compared with mechanical aortic valve replacement. *J Am Coll Cardiol*. 2018;71:1337–44.
12. El-Hamamsy I, Eryigit Z, Stevens L-M, et al. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. *Lancet*. 2010;376:524–31.
13. Martin E, Mohammadi S, Jacques F, et al. Clinical outcomes following the Ross procedure in adults: a 25-year longitudinal study. *J Am Coll Cardiol*. 2017;70:1890–9.
14. Bourguignon T, Bouquiaux-Stablo A-L, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 25-year follow-up of 450 implantations. *J Thorac Cardiovasc Surg*. 2014;148:2004–11.e1.
15. Bourguignon T, El Khoury R, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards PERIMOUNT aortic valve in patients aged 60 or younger. *Ann Thorac Surg*. 2015;100:853–9.
16. Tuzcu EM, Kapadia SR, Vemulapalli S, et al. Transcatheter aortic valve replacement of failed surgically implanted bioprostheses: the STS/ACC registry. *J Am Coll Cardiol*. 2018;72:370–82.
17. Ye J, Cheung A, Yamashita M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an 8-year single-center experience. *JACC Cardiovasc Interv*. 2015;8:1735–44.
18. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162–70.
19. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335–44.
20. Coylewright M, Forrest JK, McCabe JM, et al. TAVR in low-risk patients: FDA approval, the new NCD, and shared decision-making. *J Am Coll Cardiol*. 2020;75:1208–11.
21. Hess EP, Coylewright M, Frosch DL, et al. Implementation of shared decision making in cardiovascular care: past, present, and future. *Circ Cardiovasc Qual Outcomes*. 2014;7:797–803.
22. Weber A, Nouredine H, Englberger L, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. *J Thorac Cardiovasc Surg*. 2012;144:1075–83.
23. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152–8.
24. Chan V, Jamieson WRE, Germann E, et al. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2006;131:1267–73.
25. Dunning J, Gao H, Chambers J, et al. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use—an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. *J Thorac Cardiovasc Surg*. 2011;142:776–82.e3.
26. Stassano P, L. DT, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol*. 2009;54:1862–8.
27. Brennan JM, Edwards FH, Zhao Y, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation*. 2013;127:1647–55.
28. Banbury MK, Cosgrove DM 3rd, Thomas JD, et al. Hemodynamic stability during 17 years of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg*. 2002;73:1460–5.
29. Dellgren G, David TE, Raanani E, et al. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc Surg*. 2002;124:146–54.
30. Borger MA, Ivanov J, Armstrong S, et al. Twenty-year results of the Hancock II bioprosthesis. *J Heart Valve Dis*. 2006;15:49–55.
31. Mykén PSU, Bech-Hansen O. A 20-year experience of 1712 patients with the Biorcor porcine bioprosthesis. *J Thorac Cardiovasc Surg*. 2009;137:76–81.
32. Mazine A, El-Hamamsy I, Verma S, et al. Ross procedure in adults for cardiologists and cardiac Surgeons: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:2761–77.

3.2.4.2. Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate

1. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ*. 2016;354:i5130.
2. Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ*. 2016;354:i5065.
3. Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40:3143–53.
4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–8.
5. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–84.
6. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2565–74.
7. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–20.
8. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218–25.
9. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–705.
10. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–15.
11. Siontis KC, Killu AM. Silent and non-silent thromboembolic events after ventricular tachycardia ablation: modifiable risk with postprocedure anticoagulation? *J Cardiovasc Electrophysiol*. 2019;30:1197–9.
12. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–91.
13. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972–81.
14. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–607.
15. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686–95.
16. Burke CR, Kirkpatrick JN, Otto CM. Goals of care in patients with severe aortic stenosis. *Eur Heart J*. 2020;41:929–32.
17. Otto CM. Informed shared decisions for patients with aortic stenosis. *N Engl J Med*. 2019;380:1769–70.
18. Social Security Administration (US). Actuarial Life Table. Available at: <https://www.ssa.gov/oact/STATS/table4c6.html>. Accessed February 29, 2020.
19. Salaun E, Clavel M-A, Rodés-Cabau J, et al. Bioprosthetic aortic valve durability in the era of transcatheter aortic valve implantation. *Heart*. 2018;104:1323–32.

20. Nishimura RA, O'Gara PT, Bavaria JE, et al. 2019 AATS/ACC/ASE/SCAI/STS expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2019;73:2609–35.
21. Kumar A, Sato K, Banerjee K, et al. Hemodynamic durability of transcatheter aortic valves using the updated Valve Academic Research Consortium-2 criteria. *Catheter Cardiovasc Interv*. 2019;93:729–38.
22. Foroutan F, Guyatt GH, Otto CM, et al. Structural valve deterioration after transcatheter aortic valve implantation. *Heart*. 2017;103:1899–905.
23. Abdel-Wahab M, Neumann F-J, Mehilli J, et al. 1-Year outcomes after transcatheter aortic valve replacement with balloon-expandable versus self-expandable valves: results from the CHOICE randomized clinical trial. *J Am Coll Cardiol*. 2015;66:791–800.
24. Lytvin L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open*. 2016;6:e014327.
25. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2017;69:1313–46.
26. Abdel-Wahab M, Landt M, Neumann FJ, et al. 5-Year outcomes after TAVR with balloon-expandable versus self-expanding valves: results from the CHOICE Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2020;13:1071–82.
27. Deharo P, Bisson A, Herbert J, et al. Impact of Sapien 3 balloon-expandable versus Evolut R self-expandable transcatheter aortic valve implantation in patients with aortic stenosis: data from a nationwide analysis. *Circulation*. 2020;141:260–8.
28. Van Belle E, Vincent F, Labreuche J, et al. Balloon-expandable versus self-expanding transcatheter aortic valve replacement: a propensity-matched comparison from the FRANCE-TAVI Registry. *Circulation*. 2020;141:243–59.
29. Furer A, Chen S, Redfors B, et al. Effect of baseline left ventricular ejection fraction on 2-year outcomes after transcatheter aortic valve replacement: analysis of the PARTNER 2 trials. *Circ Heart Fail*. 2019;12:e005809.
30. Ribeiro HB, Lerakis S, Gilard M, et al. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI registry. *J Am Coll Cardiol*. 2018;71:1297–308.
31. Schewel J, Schlüter M, Schmidt T, et al. Early haemodynamic changes and long-term outcome of patients with severe low-gradient aortic stenosis after transcatheter aortic valve replacement. *EuroIntervention*. 2020;15:1181–9.
32. Maes F, Lerakis S, Barbosa Ribeiro H, et al. Outcomes from transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis and left ventricular ejection fraction less than 30%: a substudy from the TOPAS-TAVI registry. *JAMA Cardiol*. 2019;4:64–70.
33. Elmariah S, Fearon WF, Inglessis I, et al. Transapical transcatheter aortic valve replacement is associated with increased cardiac mortality in patients with left ventricular dysfunction: insights from the PARTNER I trial. *JACC Cardiovasc Interv*. 2017;10:2414–22.
34. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012;366:1696–704.
35. Kolte D, Khera S, Vemulapalli S, et al. Outcomes following urgent/emergent transcatheter aortic valve replacement: insights from the STS/ACC TVT registry. *JACC Cardiovasc Interv*. 2018;11:1175–85.
36. Nagao K, Taniguchi T, Morimoto T, et al. Acute heart failure in patients with severe aortic stenosis—insights from the CURRENT AS registry. *Circ J*. 2018;82:874–85.
37. Szerlip M, Arsanian M, Mack MC, et al. Usefulness of balloon aortic valvuloplasty in the management of patients with aortic stenosis. *Am J Cardiol*. 2017;120:1366–72.
38. Bongiovanni D, Kühl C, Bleiziffer S, et al. Emergency treatment of decompensated aortic stenosis. *Heart*. 2018;104:23–9.

4. AORTIC REGURGITATION

4.1. Acute Aortic Regurgitation

4.1.1. Diagnosis of AR

1. Hamirani YS, Dietl CA, Voyles W, et al. Acute aortic regurgitation. *Circulation*. 2012;126:1121–6.

2. Stout KK, Verrier ED. Acute valvular regurgitation. *Circulation*. 2009;119:3232–41.
3. Patel PA, Bavaria JE, Ghadimi K, et al. Aortic regurgitation in acute type-A aortic dissection: a clinical classification for the perioperative echocardiographer in the era of the functional aortic annulus. *J Cardiothorac Vasc Anesth*. 2018;32:586–97.

4.1.2. Intervention

1. Hamirani YS, Dietl CA, Voyles W, et al. Acute aortic regurgitation. *Circulation*. 2012;126:1121–6.
2. Stout KK, Verrier ED. Acute valvular regurgitation. *Circulation*. 2009;119:3232–41.
3. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. *Circulation*. 2010;121:1005–13.
4. Patel PA, Bavaria JE, Ghadimi K, et al. Aortic regurgitation in acute type-A aortic dissection: a clinical classification for the perioperative echocardiographer in the era of the functional aortic annulus. *J Cardiothorac Vasc Anesth*. 2018;32:586–97.
5. Trost JC, Hillis LD. Intra-aortic balloon counterpulsation. *Am J Cardiol*. 2006;97:1391–8.

4.3. Chronic AR

4.3.1. Diagnosis of Chronic AR

1. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303–71.
2. Detaint D, Messika-Zeitoun D, Maalouf J, et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation: a prospective study. *JACC Cardiovasc Imaging*. 2008;1:1–11.
3. Pizarro R, Bazzano OO, Overti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol*. 2011;58:1705–14.
4. Bonow RO, Picone AL, McIntosh CL, et al. Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function. *Circulation*. 1985;72:1244–56.
5. Cunha CL, Giuliani ER, Fuster V, et al. Preoperative M-mode echocardiography as a predictor of surgical results in chronic aortic insufficiency. *J Thorac Cardiovasc Surg*. 1980;79:256–65.
6. Bonow RO, Lakatos E, Maron BJ, et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*. 1991;84:1625–35.
7. Bonow RO, Rosing DR, McIntosh CL, et al. The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function. *Circulation*. 1983;68:509–17.
8. Borer JS, Hochreiter C, Herrold EM, et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. *Circulation*. 1998;97:525–34.
9. Ishii K, Hirota Y, Suwa M, et al. Natural history and left ventricular response in chronic aortic regurgitation. *Am J Cardiol*. 1996;78:357–61.
10. Scognamiglio R, Fasoli G, Dalla Volta S. Progression of myocardial dysfunction in asymptomatic patients with severe aortic insufficiency. *Clin Cardiol*. 1986;9:151–6.
11. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med*. 1994;331:689–94.
12. Siemieniczuk D, Greenberg B, Morris C, et al. Chronic aortic insufficiency: factors associated with progression to aortic valve replacement. *Ann Intern Med*. 1989;110:587–92.
13. Tornos MP, Olona M, Permanyer-Miralda G, et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. *Am Heart J*. 1995;130:333–9.
14. Tarasoutchi F, Grinberg M, Spina GS, et al. Ten-year clinical laboratory follow-up after application of a symptom-based therapeutic strategy to

patients with severe chronic aortic regurgitation of predominant rheumatic etiology. *J Am Coll Cardiol*. 2003;41:1316–24.

15. Saisho H, Arinaga K, Kikusaki S, et al. Long term results and predictors of left ventricular function recovery after aortic valve replacement for chronic aortic regurgitation. *Ann Thorac Cardiovasc Surg*. 2015;21:388–95.
16. Mentias A, Feng K, Alashi A, et al. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2016;68:2144–53.
17. Yang L-T, Michelena HI, Scott CG, et al. Outcomes in chronic hemodynamically significant aortic regurgitation and limitations of current guidelines. *J Am Coll Cardiol*. 2019;73:1741–52.
18. de Meester C, Gerber BL, Vancraeynest D, et al. Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? *JACC Cardiovasc Imaging*. 2019;12:2126–38.
19. Yang LT, Enriquez-Sarano M, Michelena HI, et al. Predictors of progression in patients with stage B aortic regurgitation. *J Am Coll Cardiol*. 2019;74:2480–92.
20. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. *Circ Cardiovasc Imaging*. 2013;6:48–57.
21. Cranney GB, Lotan CS, Dean L, et al. Left ventricular volume measurement using cardiac axis nuclear magnetic resonance imaging. Validation by calibrated ventricular angiography. *Circulation*. 1990;82:154–63.
22. Dulce MC, Mostbeck GH, O'Sullivan M, et al. Severity of aortic regurgitation: interstudy reproducibility of measurements with velocity-encoded cine MR imaging. *Radiology*. 1992;185:235–40.
23. Gelfand EV, Hughes S, Hauser TH, et al. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. *J Cardiovasc Magn Reson*. 2006;8:503–7.
24. Myerson SG, d'Arcy J, Mohiaddin R, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. *Circulation*. 2012;126:1452–60.
25. Kammerlander AA, Wiesinger M, Duca F, et al. Diagnostic and prognostic utility of cardiac magnetic resonance imaging in aortic regurgitation. *JACC Cardiovasc Imaging*. 2019;12:1474–83.
26. Teague SM, Heinsimer JA, Anderson JL, et al. Quantification of aortic regurgitation utilizing continuous wave Doppler ultrasound. *J Am Coll Cardiol*. 1986;8:592–9.
27. Attenhofer Jost CH, Turina J, Mayer K, et al. Echocardiography in the evaluation of systolic murmurs of unknown cause. *Am J Med*. 2000;108:614–20.
28. Benjelloun H, Cranney GB, Kirk KA, et al. Interstudy reproducibility of biplane cine nuclear magnetic resonance measurements of left ventricular function. *Am J Cardiol*. 1991;67:1413–20.
29. Buser PT, Auffermann W, Holt WW, et al. Noninvasive evaluation of global left ventricular function with use of cine nuclear magnetic resonance. *J Am Coll Cardiol*. 1989;13:1294–300.
30. Van Rossum AC, Visser FC, Sprenger M, et al. Evaluation of magnetic resonance imaging for determination of left ventricular ejection fraction and comparison with angiography. *Am J Cardiol*. 1988;62:628–33.

4.3.2. Medical Therapy

1. Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med*. 2005;353:1342–9.
2. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med*. 1994;331:689–94.
3. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–646.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–61.
5. Elder DHJ, Wei L, Swzekowski BR, et al. The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have aortic regurgitation: a large population cohort study. *J Am Coll Cardiol*. 2011;58:2084–91.
6. Fioretti P, Benussi B, Scardi S, et al. Afterload reduction with nifedipine in aortic insufficiency. *Am J Cardiol*. 1982;49:1728–32.

7. Lin M, Chiang HT, Lin SL, et al. Vasodilator therapy in chronic asymptomatic aortic regurgitation: enalapril versus hydralazine therapy. *J Am Coll Cardiol*. 1994;24:1046–53.
8. Søndergaard L, Aldershvile J, Hildebrandt P, et al. Vasodilatation with felodipine in chronic asymptomatic aortic regurgitation. *Am Heart J*. 2000;139:667–74.
9. Sampat U, Varadarajan P, Turk R, et al. Effect of beta-blocker therapy on survival in patients with severe aortic regurgitation results from a cohort of 756 patients. *J Am Coll Cardiol*. 2009;54:452–7.

4.3.3. Timing of Intervention

1. Bonow RO, Borer JS, Rosing DR, et al. Preoperative exercise capacity in symptomatic patients with aortic regurgitation as a predictor of postoperative left ventricular function and long-term prognosis. *Circulation*. 1980;62:1280–90.
2. Klodas E, Enriquez-Sarano M, Tajik AJ, et al. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol*. 1997;30:746–52.
3. Chaliki HP, Mohty D, Avierinos J-F, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation*. 2002;106:2687–93.
4. Tornos P, Sambola A, Permanyer-Miralda G, et al. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol*. 2006;47:1012–7.
5. Bhudia SK, McCarthy PM, Kumpati GS, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. *J Am Coll Cardiol*. 2007;49:1465–71.
6. Fiedler AG, Bhambhani V, Laikhter E, et al. Aortic valve replacement associated with survival in severe regurgitation and low ejection fraction. *Heart*. 2018;104:835–40.
7. Kaneko T, Ejiofor JI, Neely RC, et al. Aortic regurgitation with markedly reduced left ventricular function is not a contraindication for aortic valve replacement. *Ann Thorac Surg*. 2016;102:41–7.
8. Greves J, Rahimtoola SH, McAnulty JH, et al. Preoperative criteria predictive of late survival following valve replacement for severe aortic regurgitation. *Am Heart J*. 1981;101:300–8.
9. Forman R, Firth BG, Barnard MS. Prognostic significance of preoperative left ventricular ejection fraction and valve lesion in patients with aortic valve replacement. *Am J Cardiol*. 1980;45:1120–5.
10. Bonow RO, Picone AL, McIntosh CL, et al. Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function. *Circulation*. 1985;72:1244–56.
11. Cormier B, Vahanian A, Luxureau P, et al. Should asymptomatic or mildly symptomatic aortic regurgitation be operated on? *Z Kardiol*. 1986;75(suppl 2):141–5.
12. Klodas E, Enriquez-Sarano M, Tajik AJ, et al. Aortic regurgitation complicated by extreme left ventricular dilation: long-term outcome after surgical correction. *J Am Coll Cardiol*. 1996;27:670–7.
13. Saisho H, Arinaga K, Kikusaki S, et al. Long term results and predictors of left ventricular function recovery after aortic valve replacement for chronic aortic regurgitation. *Ann Thorac Cardiovasc Surg*. 2015;21:388–95.
14. Mentias A, Feng K, Alashi A, et al. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2016;68:2144–53.
15. Yang L-T, Michelena HI, Scott CG, et al. Outcomes in chronic hemodynamically significant aortic regurgitation and limitations of current guidelines. *J Am Coll Cardiol*. 2019;73:1741–52.
16. de Meester C, Gerber BL, Vancraeynest D, et al. Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? *JACC Cardiovasc Imaging*. 2019;12:2126–38.
17. Bonow RO, Lakatos E, Maron BJ, et al. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*. 1991;84:1625–35.
18. Detaint D, Messika-Zeitoun D, Maalouf J, et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation: a prospective study. *JACC Cardiovasc Imaging*. 2008;1:1–11.
19. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol*. 2011;58:1705–14.
20. Tornos MP, Olona M, Permanyer-Miralda G, et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. *Am Heart J*. 1995;130:333–9.

21. Tarasoutchi F, Grinberg M, Spina GS, et al. Ten-year clinical laboratory follow-up after application of a symptom-based therapeutic strategy to patients with severe chronic aortic regurgitation of predominant rheumatic etiology. *J Am Coll Cardiol*. 2003;41:1316–24.
22. Kumpuris AG, Quinones MA, Waggoner AD, et al. Importance of preoperative hypertrophy, wall stress and end-systolic dimension as echocardiographic predictors of normalization of left ventricular dilatation after valve replacement in chronic aortic insufficiency. *Am J Cardiol*. 1982;49:1091–100.
23. Fioretti P, Roelandt J, Bos RJ, et al. Echocardiography in chronic aortic insufficiency. Is valve replacement too late when left ventricular end-systolic dimension reaches 55 mm? *Circulation*. 1983;67:216–21.
24. Stone PH, Clark RD, Goldschlager N, et al. Determinants of prognosis of patients with aortic regurgitation who undergo aortic valve replacement. *J Am Coll Cardiol*. 1984;3:1118–26.
25. Zhang Z, Yang J, Yu Y, et al. Preoperative ejection fraction determines early recovery of left ventricular end-diastolic dimension after aortic valve replacement for chronic severe aortic regurgitation. *J Surg Res*. 2015;196:49–55.
26. Murashita T, Schaff HV, Suri RM, et al. Impact of left ventricular systolic function on outcome of correction of chronic severe aortic valve regurgitation: implications for timing of surgical intervention. *Ann Thorac Surg*. 2017;103:1222–8.
27. Wang Y, Jiang W, Liu J, et al. Early surgery versus conventional treatment for asymptomatic severe aortic regurgitation with normal ejection fraction and left ventricular dilatation. *Eur J Cardiothorac Surg*. 2017;52:118–24.
28. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med*. 1994;331:689–94.
29. Sawaya FJ, Deutsch MA, Seiffert M, et al. Safety and efficacy of transcatheter aortic valve replacement in the treatment of pure aortic regurgitation in native valves and failing surgical bioprostheses: results from an International Registry Study. *JACC Cardiovasc Interv*. 2017;10:1048–56.
30. Roy DA, Schaefer U, Guetta V, et al. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol*. 2013;61:1577–84.
31. Seiffert M, Bader R, Kappert U, et al. Initial German experience with transcatheter implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. *JACC Cardiovasc Interv*. 2014;7:1168–74.
32. Jiang J, Liu X, He Y, et al. Transcatheter aortic valve replacement for pure native aortic valve regurgitation: a systematic review. *Cardiology*. 2018;141:132–40.
33. Aicher D, Kuniyara T, Abou Issa O, et al. Valve configuration determines long-term results after repair of the bicuspid aortic valve. *Circulation*. 2011;123:178–85.
34. David TE, Armstrong S, Ivanov J, et al. Aortic valve sparing operations: an update. *Ann Thorac Surg*. 1999;67:1840–2.
35. Kallenbach K, Hagl C, Walles T, et al. Results of valve-sparing aortic root reconstruction in 158 consecutive patients. *Ann Thorac Surg*. 2002;74:2026–32.
36. Pettersson GB, Crucean AC, Savage R, et al. Toward predictable repair of regurgitant aortic valves: a systematic morphology-directed approach to bicommissural repair. *J Am Coll Cardiol*. 2008;52:40–9.
37. de Kerchove L, Boodhwani M, Glineur D, et al. Valve repair-root replacement with the reimplantation technique to increase the durability of bicuspid aortic valve repair. *J Thorac Cardiovasc Surg*. 2011;142:1430–8.
38. Kari FA, Liang DH, Kvitting J-PE, et al. Tirone David valve-sparing aortic root replacement and cusp repair for bicuspid aortic valve disease. *J Thorac Cardiovasc Surg*. 2013;145:S35–40.e1–2.
39. Ouzounian M, Rao V, Manlihot C, et al. Valve-sparing root replacement compared with composite valve graft procedures in patients with aortic root dilation. *J Am Coll Cardiol*. 2016;68:1838–47.
40. Gleason TG. New graft formulation and modification of the David reimplantation technique. *J Thorac Cardiovasc Surg*. 2005;130:601–3.
41. le Polain de Waroux JB, Pouleur AC, Robert A, et al. Mechanisms of recurrent aortic regurgitation after aortic valve repair: predictive value of intraoperative transesophageal echocardiography. *JACC Cardiovasc Imaging*. 2009;2:931–9.
42. Boodhwani M, de Kerchove L, Glineur D, et al. Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. *J Thorac Cardiovasc Surg*. 2009;137:286–94.
43. Borow KM, Green LH, Mann T, et al. End-systolic volume as a predictor of postoperative left ventricular performance in volume overload from valvular regurgitation. *Am J Med*. 1980;68:655–63.
44. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol*. 2011;58:1705–14.
45. Myerson SG, d'Arcy J, Mohiaddin R, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. *Circulation*. 2012;126:1452–60.
46. Kammerlander AA, Wiesinger M, Duca F, et al. Diagnostic and prognostic utility of cardiac magnetic resonance imaging in aortic regurgitation. *JACC Cardiovasc Imaging*. 2019;12:1474–83.
47. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
48. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, et al. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:29.
49. Lee JKT, Franzone A, Lanz J, et al. Early detection of subclinical myocardial damage in chronic aortic regurgitation and strategies for timely treatment of asymptomatic patients. *Circulation*. 2018;137:184–96.
50. Alashi A, Mentias A, Abdallah A, et al. Incremental prognostic utility of left ventricular global longitudinal strain in asymptomatic patients with significant chronic aortic regurgitation and preserved left ventricular ejection fraction. *JACC Cardiovasc Imaging*. 2018;11:673–82.
51. Olsen NT, Sogaard P, Larsson HB, et al. Speckle-tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery. *JACC Cardiovasc Imaging*. 2011;4:223–30.
52. Dujardin KS, Enriquez-Sarano M, Schaff HV, et al. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation*. 1999;99:1851–7.
53. Bonow RO, Dodd JT, Maron BJ, et al. Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. *Circulation*. 1988;78:1108–20.
54. Carabello BA, Williams H, Gash AK, et al. Hemodynamic predictors of outcome in patients undergoing valve replacement. *Circulation*. 1986;74:1309–16.
55. Cunha CL, Giuliani ER, Fuster V, et al. Preoperative M-mode echocardiography as a predictor of surgical results in chronic aortic insufficiency. *J Thorac Cardiovasc Surg*. 1980;79:256–65.
56. Daniel WG, Hood WP Jr, Siart A, et al. Chronic aortic regurgitation: reassessment of the prognostic value of preoperative left ventricular end-systolic dimension and fractional shortening. *Circulation*. 1985;71:669–80.
57. Henry WL, Bonow RO, Borer JS, et al. Observations on the optimum time for operative intervention for aortic regurgitation. I. Evaluation of the results of aortic valve replacement in symptomatic patients. *Circulation*. 1980;61:471–83.
58. Michel PL, lung B, Abou Jaoude S, et al. The effect of left ventricular systolic function on long term survival in mitral and aortic regurgitation. *J Heart Valve Dis*. 1995;4(suppl 2):S160–8.
59. Sheiban I, Trevi GP, Casarotto D, et al. Aortic valve replacement in patients with aortic incompetence. Preoperative parameters influencing long-term results. *Z Kardiol*. 1986;75(suppl 2):146–54.
60. Taniguchi K, Nakano S, Hirose H, et al. Preoperative left ventricular function: minimal requirement for successful late results of valve replacement for aortic regurgitation. *J Am Coll Cardiol*. 1987;10:510–8.
61. Turina J, Milincic J, Seifert B, et al. Valve replacement in chronic aortic regurgitation. True predictors of survival after extended follow-up. *Circulation*. 1998;98:II100–6.
62. Gaasch WH, Carroll JD, Levine HJ, et al. Chronic aortic regurgitation: prognostic value of left ventricular end-systolic dimension and end-diastolic radius/thickness ratio. *J Am Coll Cardiol*. 1983;1:775–82.

5. BICUSPID AORTIC VALVE

5.1. BAV and Associated Aortopathy

5.1.1. Diagnosis and Follow-Up of BAV

5.1.1.1. Diagnostic Testing: Initial Diagnosis

1. Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart*. 2017;103:1323–30.

2. Keane MG, Wieggers SE, Plappert T, et al. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. *Circulation*. 2000;102:1135–9.
3. Schaefer BM, Lewin MB, Stout KK, et al. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. *Heart*. 2008;94:1634–8.
4. Goldstein SA, Evangelista A, Abbasa S, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2015;28:119–82.
5. Kang J-W, Song HG, Yang DH, et al. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. *JACC Cardiovasc Imaging*. 2013;6:150–61.
6. Kerstjens-Frederikse WS, Du Marchie Sarvaas GJ, Ruiter JS, et al. Left ventricular outflow tract obstruction: should cardiac screening be offered to first-degree relatives? *Heart*. 2011;97:1228–32.
7. Pachulski RT, Weinberg AL, Chan KL. Aortic aneurysm in patients with functionally normal or minimally stenotic bicuspid aortic valve. *Am J Cardiol*. 1991;67:781–2.
8. Hahn RT, Roman MJ, Mogtader AH, et al. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol*. 1992;19:283–8.
9. Nistri S, Sorbo MD, Marin M, et al. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart*. 1999;82:19–22.
10. Novaro GM, Tiong IY, Pearce GL, et al. Features and predictors of ascending aortic dilatation in association with a congenital bicuspid aortic valve. *Am J Cardiol*. 2003;92:99–101.
11. Michelena HI, Prakash SK, Della Corte A, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation*. 2014;129:2691–704.
- Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27–129.
3. Elefteriades JA. Natural history of thoracic aortic aneurysms: indications for surgery, and surgical versus nonsurgical risks. *Ann Thorac Surg*. 2002;74:S1877–80.
4. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg*. 2002;73:17–27.
5. Russo CF, Mazzetti S, Garatti A, et al. Aortic complications after bicuspid aortic valve replacement: long-term results. *Ann Thorac Surg*. 2002;74:S1773–6.
6. Borger MA, Preston M, Ivanov J, et al. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? *J Thorac Cardiovasc Surg*. 2004;128:677–83.
7. Svensson LG, Kim K-H, Blackstone EH, et al. Bicuspid aortic valve surgery with proactive ascending aorta repair. *J Thorac Cardiovasc Surg*. 2011;142:622–9, 9.e1–3.
8. Beckerman Z, Kayatta MO, McPherson L, et al. Bicuspid aortic valve repair in the setting of severe aortic insufficiency. *J Vis Surg*. 2018;4:101.
9. David TE, Feindel CM, David CM, et al. A quarter of a century of experience with aortic valve-sparing operations. *J Thorac Cardiovasc Surg*. 2014;148:872–9.
10. Davies RR, Kaple RK, Mandapati D, et al. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. *Ann Thorac Surg*. 2007;83:1338–44.
11. Ergin MA, Spielvogel D, Apaydin A, et al. Surgical treatment of the dilated ascending aorta: when and how? *Ann Thorac Surg*. 1999;67:1834–9.
12. Svensson LG, Kim K-H, Lytle BW, et al. Relationship of aortic cross-sectional area to height ratio and the risk of aortic dissection in patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg*. 2003;126:892–3.
13. Yasuda H, Nakatani S, Stugaard M, et al. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. *Circulation*. 2003;108(suppl 1):II291–4.
14. Park CB, Greeson KL, Suri RM, et al. Fate of nonreplaced sinuses of Valsalva in bicuspid aortic valve disease. *J Thorac Cardiovasc Surg*. 2011;142:278–84.
15. Svensson LG, Adams DH, Bonow RO, et al. Aortic valve and ascending aorta guidelines for management and quality measures. *Ann Thorac Surg*. 2013;95:S1–66.

5.1.1.2. Diagnostic Testing: Routine Follow-Up

1. Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart*. 2017;103:1323–30.
2. Ferencik M, Pape LA. Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. *Am J Cardiol*. 2003;92:43–6.
3. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA*. 2011;306:1104–12.
4. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg*. 2002;73:17–27.
5. Masri A, Kalahasti V, Alkharabsheh S, et al. Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg*. 2016;151:1650–9.e1.
6. McKellar SH, Michelena HI, Li Z, et al. Long-term risk of aortic events following aortic valve replacement in patients with bicuspid aortic valves. *Am J Cardiol*. 2010;106:1626–33.
7. Girdauskas E, Disha K, Borger MA, et al. Long-term prognosis of ascending aortic aneurysm after aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Thorac Cardiovasc Surg*. 2014;147:276–82.
8. Novaro GM, Griffin BP. Congenital bicuspid aortic valve and rate of ascending aortic dilatation. *Am J Cardiol*. 2004;93:525–6.
9. Davies RR, Kaple RK, Mandapati D, et al. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. *Ann Thorac Surg*. 2007;83:1338–44.
10. Girdauskas E, Rouman M, Disha K, et al. The fate of mild-to-moderate proximal aortic dilatation after isolated aortic valve replacement for bicuspid aortic valve stenosis: a magnetic resonance imaging follow-up study. *Eur J Cardiothorac Surg*. 2016;49:e80–6.
11. Borger MA, Fedak PWM, Stephens EH, et al. The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve-related aortopathy: Full online-only version. *J Thorac Cardiovasc Surg*. 2018;156:e41–74.

5.1.2. Interventions for Patients With BAV

5.1.2.1. Intervention: Repair or Replacement of the Aorta

1. Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart*. 2017;103:1323–30.
2. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of

5.1.2.2. Intervention: Repair or Replacement of the Aortic Valve

1. David TE, Feindel CM, David CM, et al. A quarter of a century of experience with aortic valve-sparing operations. *J Thorac Cardiovasc Surg*. 2014;148:872–9.
2. Masri A, Kalahasti V, Alkharabsheh S, et al. Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg*. 2016;151:1650–9.e1.
3. Schneider U, Feldner SK, Hofmann C, et al. Two decades of experience with root remodeling and valve repair for bicuspid aortic valves. *J Thorac Cardiovasc Surg*. 2017;153:S65–71.
4. Takagi H, Hari Y, Kawai N, et al. Meta-analysis of transcatheter aortic valve implantation for bicuspid versus tricuspid aortic valves. *J Cardiol*. 2019;74:40–8.
5. Kanjanahattakij N, Horn B, Vutthikraivit W, et al. Comparing outcomes after transcatheter aortic valve replacement in patients with stenotic bicuspid and tricuspid aortic valve: a systematic review and meta-analysis. *Clin Cardiol*. 2018;41:896–902.
6. Makkar RR, Yoon S-H, Leon MB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. *JAMA*. 2019;321:2193–202.
7. Beckerman Z, Kayatta MO, McPherson L, et al. Bicuspid aortic valve repair in the setting of severe aortic insufficiency. *J Vis Surg*. 2018;4:101.

6. MITRAL STENOSIS

1. Eleid MF, Nishimura RA, Lennon RJ, et al. Left ventricular diastolic dysfunction in patients with mitral stenosis undergoing percutaneous mitral balloon valvotomy. *Mayo Clin Proc*. 2013;88:337–44.

- Nunes MCP, Tan TC, Elmariah S, et al. Net atrioventricular compliance is an independent predictor of cardiovascular death in mitral stenosis. *Heart*. 2017;103:1891–8.
- Abramowitz Y, Jilalawi H, Chakravarty T, et al. Mitral annulus calcification. *J Am Coll Cardiol*. 2015;66:1934–41.
- Sud K, Agarwal S, Parashar A, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. *Circulation*. 2016;133:1594–604.
- Bertrand PB, Mihos CG, Yucel E. Mitral annular calcification and calcific mitral stenosis: therapeutic challenges and considerations. *Curr Treat Options Cardiovasc Med*. 2019;21:19.

6.1. Stages of MS

- Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.

6.2. Rheumatic MS

6.2.1. Diagnosis and Follow-Up of Rheumatic MS

6.2.1.1. Diagnostic Testing: Initial Diagnosis

- Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.
- Nunes MCP, Tan TC, Elmariah S, et al. The echo score revisited: impact of incorporating commissural morphology and leaflet displacement to the prediction of outcome for patients undergoing percutaneous mitral valvuloplasty. *Circulation*. 2014;129:886–95.
- Cannan CR, Nishimura RA, Reeder GS, et al. Echocardiographic assessment of commissural calcium: a simple predictor of outcome after percutaneous mitral balloon valvotomy. *J Am Coll Cardiol*. 1997;29:175–80.
- Ellis K, Ziada KM, Vivekananthan D, et al. Transthoracic echocardiographic predictors of left atrial appendage thrombus. *Am J Cardiol*. 2006;97:421–5.
- Kronzon I, Tunick PA, Glassman E, et al. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. *J Am Coll Cardiol*. 1990;16:1320–2.
- Tessier P, Mercier LA, Burelle D, et al. Results of percutaneous mitral commissurotomy in patients with a left atrial appendage thrombus detected by transesophageal echocardiography. *J Am Soc Echocardiogr*. 1994;7:394–9.
- Gianstefani S, Monaghan MJ. Accurate assessment of the true mitral valve area in rheumatic mitral stenosis. *Heart*. 2013;99:219–21.
- Min S-Y, Song J-M, Kim Y-J, et al. Discrepancy between mitral valve areas measured by two-dimensional planimetry and three-dimensional transesophageal echocardiography in patients with mitral stenosis. *Heart*. 2013;99:253–8.
- Nishimura RA, Rihal CS, Tajik AJ, et al. Accurate measurement of the transmitral gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol*. 1994;24:152–8.
- Abascal VM, Wilkins GT, O'Shea JP, et al. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation*. 1990;82:448–56.
- Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J*. 1988;60:299–308.
- Sutaria N, Northridge DB, Shaw TR. Significance of commissural calcification on outcome of mitral balloon valvotomy. *Heart*. 2000;84:398–402.
- Gajjala OR, Durgaprasad R, Velam V, et al. New integrated approach to percutaneous mitral valvuloplasty combining Wilkins score with commissural calcium score and commissural area ratio. *Echocardiography*. 2017;34:1284–91.
- Thomas JD, Wilkins GT, Choong CY, et al. Inaccuracy of mitral pressure half-time immediately after percutaneous mitral valvotomy. Dependence on transmitral gradient and left atrial and ventricular compliance. *Circulation*. 1988;78:980–93.
- Rinkevich D, Lessick J, Mutlak D, et al. Natural history of moderate mitral valve stenosis. *Isr Med Assoc J*. 2003;5:15–8.
- Sagie A, Freitas N, Padial LR, et al. Doppler echocardiographic assessment of long-term progression of mitral stenosis in 103 patients: valve area and right heart disease. *J Am Coll Cardiol*. 1996;28:472–9.

6.2.1.4. Diagnostic Testing: Cardiac Catheterization

- Nishimura RA, Rihal CS, Tajik AJ, et al. Accurate measurement of the transmitral gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol*. 1994;24:152–8.
- Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. *Am Heart J*. 1951;41:1–29.
- Gorlin WB, Gorlin R. A generalized formulation of the Gorlin formula for calculating the area of the stenotic mitral valve and other stenotic cardiac valves. *J Am Coll Cardiol*. 1990;15:246–7.

6.2.1.5. Diagnostic Testing: Exercise Testing

- Cheitlin MD. Stress echocardiography in mitral stenosis: when is it useful? *J Am Coll Cardiol*. 2004;43:402–4.
- Cherix EC, Pieters FA, Janssen JH, et al. Value of exercise Doppler-echocardiography in patients with mitral stenosis. *Int J Cardiol*. 1994;45:219–26.
- Grimaldi A, Olivetto I, Figini F, et al. Dynamic assessment of “valvular reserve capacity” in patients with rheumatic mitral stenosis. *Eur Heart J Cardiovasc Imaging*. 2012;13:476–82.
- Suh WM, Kern MJ. Addressing the hemodynamic dilemma of combined mitral and aortic stenosis. *Catheter Cardiovasc Interv*. 2008;71:944–9.
- Reis G, Motta MS, Barbosa MM, et al. Dobutamine stress echocardiography for noninvasive assessment and risk stratification of patients with rheumatic mitral stenosis. *J Am Coll Cardiol*. 2004;43:393–401.
- Roshdy HS, Meshrif AM, El-Dosouky II. Value of the mitral valve resistance in evaluation of symptomatic patients with mild and moderate mitral stenosis—a dobutamine stress echocardiographic study. *Echocardiography*. 2014;31:347–52.

6.2.2. Medical Therapy

- Kim JY, Kim S-H, Myong J-P, et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol*. 2019;73:1123–31.
- Giugliano RP, O'Gara PT. DOACs in Patients with mitral stenosis and atrial fibrillation: time for a randomized clinical trial. *J Am Coll Cardiol*. 2019;73:1132–4.
- Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br Heart J*. 1962;24:349–57.
- Rowe JC, Bland EF, Sprague HB, et al. The course of mitral stenosis without surgery: ten- and twenty-year perspectives. *Ann Intern Med*. 1960;52:741–9.
- Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br Med J*. 1964;1:1209–12.
- Wilson JK, Greenwood WF. The natural history of mitral stenosis. *Can Med Assoc J*. 1954;71:323–31.
- Omran H, Rang B, Schmidt H, et al. Incidence of left atrial thrombi in patients in sinus rhythm and with a recent neurologic deficit. *Am Heart J*. 2000;140:658–62.
- Yusuf J, Goyal M, Mukhopadhyay S, et al. Effect of heart rate control on coagulation status in patients of rheumatic mitral stenosis with atrial fibrillation—a pilot study. *Indian Heart J*. 2015;67(suppl 2):S40–5.
- Rigolin VH, Higgenbotham MB, Robiolio PA, et al. Effect of inadequate cardiac output reserve on exercise tolerance in patients with moderate mitral stenosis. *Am J Cardiol*. 1997;80:236–40.
- Laufer-Perl M, Gura Y, Shimiaie J, et al. Mechanisms of effort intolerance in patients with rheumatic mitral stenosis: combined echocardiography and cardiopulmonary stress protocol. *JACC Cardiovasc Imaging*. 2017;10:622–33.
- Kitzman DW, Upadhyay B, Zhao D. New concepts in an old disease: exercise intolerance in moderate mitral stenosis. *JACC Cardiovasc Imaging*. 2017;10:634–6.
- Saggu DK, Narain VS, Dwivedi SK, et al. Effect of ivabradine on heart rate and duration of exercise in patients with mild-to-moderate mitral stenosis: a randomized comparison with metoprolol. *J Cardiovasc Pharmacol*. 2015;65:552–4.
- Parakh N, Chaturvedi V, Kurian S, et al. Effect of ivabradine vs atenolol on heart rate and effort tolerance in patients with mild to moderate mitral stenosis and normal sinus rhythm. *J Card Fail*. 2012;18:282–8.

6.2.1.3. Diagnostic Testing: Routine Follow-Up

- Horstkotte D, Niehues R, Strauer BE. Pathomorphological aspects, aetiology and natural history of acquired mitral valve stenosis. *Eur Heart J*. 1991;12(suppl B):55–60.

14. Agrawal V, Kumar N, Lohiya B, et al. Metoprolol vs ivabradine in patients with mitral stenosis in sinus rhythm. *Int J Cardiol*. 2016;221:562–6.
15. Rajesh GN, Sajeev K, Sajeev CG, et al. A comparative study of ivabradine and atenolol in patients with moderate mitral stenosis in sinus rhythm. *Indian Heart J*. 2016;68:311–5.
16. lung B, Leenhardt A, Extramiana F. Management of atrial fibrillation in patients with rheumatic mitral stenosis. *Heart*. 2018;104:1062–8.
17. Krishnamoorthy KM. Incidence and predictors of left atrial thrombus in patients with rheumatic mitral stenosis and sinus rhythm: a transesophageal echocardiographic study. *Echocardiography*. 2012;29:876–7.
18. Manjunath CN, Srinivasa KH, Panneerselvam A, et al. Incidence and predictors of left atrial thrombus in patients with rheumatic mitral stenosis and sinus rhythm: a transesophageal echocardiographic study. *Echocardiography*. 2011;28:457–60.
19. Keenan NG, Cuffe C, Cimadevilla C, et al. Usefulness of left atrial volume versus diameter to assess thromboembolic risk in mitral stenosis. *Am J Cardiol*. 2010;106:1152–6.
20. Cannan CR, Nishimura RA, Reeder GS, et al. Echocardiographic assessment of commissural calcium: a simple predictor of outcome after percutaneous mitral balloon valvotomy. *J Am Coll Cardiol*. 1997;29:175–80.
21. Apostolakis EE, Baikoussis NG. Methods of estimation of mitral valve regurgitation for the cardiac surgeon. *J Cardiothorac Surg*. 2009;4:34.
22. Badheka AO, Shah N, Ghatak A, et al. Balloon mitral valvuloplasty in the United States: a 13-year perspective. *Am J Med*. 2014;127:1126 e1–12.
23. Abascal VM, Wilkins GT, O'Shea JP, et al. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation*. 1990;82:448–56.
24. Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J*. 1988;60:299–308.
25. Sutaria N, Northridge DB, Shaw TR. Significance of commissural calcification on outcome of mitral balloon valvotomy. *Heart*. 2000;84:398–402.
26. Gajjala OR, Durgaprasad R, Velam V, et al. New integrated approach to percutaneous mitral valvuloplasty combining Wilkins score with commissural calcium score and commissural area ratio. *Echocardiography*. 2017;34:1284–91.
27. Cho I-J, Hong G-R, Lee SH, et al. Differences in characteristics, left atrial reverse remodeling, and functional outcomes after mitral valve replacement in patients with low-gradient very severe mitral stenosis. *J Am Soc Echocardiogr*. 2016;29:759–67.
28. El Sabbagh A, Reddy YNV, Barros-Gomes S, et al. Low-gradient severe mitral stenosis: hemodynamic profiles, clinical characteristics, and outcomes. *J Am Heart Assoc*. 2019;8:e010736.
29. Nunes MCP, Tan TC, Elmiah S, et al. Net atrioventricular compliance is an independent predictor of cardiovascular death in mitral stenosis. *Heart*. 2017;103:1891–8.
30. Eleid MF, Nishimura RA, Lennon RJ, et al. Left ventricular diastolic dysfunction in patients with mitral stenosis undergoing percutaneous mitral balloon valvotomy. *Mayo Clin Proc*. 2013;88:337–44.
31. Cho I-J, Chang H-J, Lee SY, et al. Differential impact of net atrioventricular compliance on clinical outcomes in patients with mitral stenosis according to cardiac rhythm. *J Am Soc Echocardiogr*. 2017;30:552–60.
32. Ellis LB, Singh JB, Morales DD, et al. Fifteen-to twenty-year study of one thousand patients undergoing closed mitral valvuloplasty. *Circulation*. 1973;48:357–64.
33. Finnegan JO, Gray DC, MacVaugh H 3rd, et al. The open approach to mitral commissurotomy. *J Thorac Cardiovasc Surg*. 1974;67:75–82.
34. Gross RI, Cunningham JN Jr, Snively SL, et al. Long-term results of open radical mitral commissurotomy: ten year follow-up study of 202 patients. *Am J Cardiol*. 1981;47:821–5.
35. Halseth WL, Elliott DP, Walker EL, et al. Open mitral commissurotomy. A modern re-evaluation. *J Thorac Cardiovasc Surg*. 1980;80:842–8.
36. John S, Bashi VV, Jairaj PS, et al. Closed mitral valvotomy: early results and long-term follow-up of 3724 consecutive patients. *Circulation*. 1983;68:891–6.
37. Mullin MJ, Engelman RM, Isom OW, et al. Experience with open mitral commissurotomy in 100 consecutive patients. *Surgery*. 1974;76:974–82.
38. Song H, Kang D-H, Kim JH, et al. Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation. *Circulation*. 2007;116:1246–50.
39. Hart SA, Krasuski RA, Wang A, et al. Pulmonary hypertension and elevated transpulmonary gradient in patients with mitral stenosis. *J Heart Valve Dis*. 2010;19:708–15.
40. Coutinho GF, Antunes MJ. Surgery for mitral stenosis in patients with pulmonary hypertension: how far can we go? *J Thorac Cardiovasc Surg*. 2016;152:302–3.
41. Mahfouz RA. Impact of pulmonary artery stiffness on right ventricular function and tricuspid regurgitation after successful percutaneous balloon mitral valvuloplasty: the importance of early intervention. *Echocardiography*. 2012;29:1157–63.
42. Arat N, Altay H, Korkmaz S, et al. The effect of baseline pulmonary artery pressure on right ventricular functions after mitral balloon valvuloplasty for rheumatic mitral stenosis: a tissue Doppler imaging study. *Turk Kardiyol Dern Ars*. 2008;36:223–30.
43. Vincens JJ, Temizer D, Post JR, et al. Long-term outcome of cardiac surgery in patients with mitral stenosis and severe pulmonary hypertension. *Circulation*. 1995;92:II137–42.
44. lung B, Leenhardt A, Extramiana F. Management of atrial fibrillation in patients with rheumatic mitral stenosis. *Heart*. 2018;104:1062–8.
45. Cheitlin MD. Stress echocardiography in mitral stenosis: when is it useful? *J Am Coll Cardiol*. 2004;43:402–4.

6.2.3. Intervention

1. Nunes MCP, Tan TC, Elmiah S, et al. The echo score revisited: impact of incorporating commissural morphology and leaflet displacement to the prediction of outcome for patients undergoing percutaneous mitral valvuloplasty. *Circulation*. 2014;129:886–95.
2. Bouleti C, lung B, Laouénan C, et al. Late results of percutaneous mitral commissurotomy up to 20 years: development and validation of a risk score predicting late functional results from a series of 912 patients. *Circulation*. 2012;125:2119–27.
3. Meneguz-Moreno RA, Costa JR Jr, Gomes NL, et al. Very long term follow-up after percutaneous balloon mitral valvuloplasty. *JACC Cardiovasc Interv*. 2018;11:1945–52.
4. Rifaie O, Abdel-Dayem MK, Ramzy A, et al. Percutaneous mitral valvotomy versus closed surgical commissurotomy. Up to 15 years of follow-up of a prospective randomized study. *J Cardiol*. 2009;53:28–34.
5. Cardoso LF, Grinberg M, Pomerantzeff PMA, et al. Comparison of open commissurotomy and balloon valvuloplasty in mitral stenosis. A five-year follow-up. *Arq Bras Cardiol*. 2004;83:248–52; 3–7.
6. Cotrufo M, Renzulli A, Ismeno G, et al. Percutaneous mitral commissurotomy versus open mitral commissurotomy: a comparative study. *Eur J Cardiothorac Surg*. 1999;15:646–51.
7. Song J-K, Kim M-J, Yun S-C, et al. Long-term outcomes of percutaneous mitral balloon valvuloplasty versus open cardiac surgery. *J Thorac Cardiovasc Surg*. 2010;139:103–10.
8. Arora R, Nair M, Kalra GS, et al. Immediate and long-term results of balloon and surgical closed mitral valvotomy: a randomized comparative study. *Am Heart J*. 1993;125:1091–4.
9. Ben FM, Ayari M, Maatouk F, et al. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation*. 1998;97:245–50.
10. Patel JJ, Shama D, Mitha AS, et al. Balloon valvuloplasty versus closed commissurotomy for pliable mitral stenosis: a prospective hemodynamic study. *J Am Coll Cardiol*. 1991;18:1318–22.
11. Reyes VP, Raju BS, Wynne J, et al. Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med*. 1994;331:961–7.
12. Turi ZG, Reyes VP, Raju BS, et al. Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis. A prospective, randomized trial. *Circulation*. 1991;83:1179–85.
13. Reichart DT, Sodani R, Zenker R, et al. Long-term (≤ 50 years) results of patients after mitral valve commissurotomy—a single-center experience. *J Thorac Cardiovasc Surg*. 2012;143:596–8.
14. Yang B, DeBenedictis C, Watt T, et al. The impact of concomitant pulmonary hypertension on early and late outcomes following surgery for mitral stenosis. *J Thorac Cardiovasc Surg*. 2016;152:394–400.e1.
15. Demirkan B, Guray Y, Guray U, et al. The acute effect of percutaneous mitral balloon valvuloplasty on atrial electromechanical delay and P-wave dispersion in patients with mitral stenosis. *Herz*. 2013;38:210–5.
16. Aviles RJ, Nishimura RA, Pellikka PA, et al. Utility of stress Doppler echocardiography in patients undergoing percutaneous mitral balloon valvotomy. *J Am Soc Echocardiogr*. 2001;14:676–81.
17. Bouleti C, lung B, Himbert D, et al. Relationship between valve calcification and long-term results of percutaneous mitral commissurotomy for rheumatic mitral stenosis. *Circ Cardiovasc Interv*. 2014;7:381–9.
18. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.

45. Cheriex EC, Pieters FA, Janssen JH, et al. Value of exercise Doppler-echocardiography in patients with mitral stenosis. *Int J Cardiol.* 1994;45:219–26.
46. Grimaldi A, Olivetto I, Figini F, et al. Dynamic assessment of “valvular reserve capacity” in patients with rheumatic mitral stenosis. *Eur Heart J Cardiovasc Imaging.* 2012;13:476–82.
47. Suh WM, Kern MJ. Addressing the hemodynamic dilemma of combined mitral and aortic stenosis. *Catheter Cardiovasc Interv.* 2008;71:944–9.
48. Reis G, Motta MS, Barbosa MM, et al. Dobutamine stress echocardiography for noninvasive assessment and risk stratification of patients with rheumatic mitral stenosis. *J Am Coll Cardiol.* 2004;43:393–401.

6.3. Nonrheumatic Calcific MS

1. Abramowitz Y, Jilalawi H, Chakravarty T, et al. Mitral annulus calcification. *J Am Coll Cardiol.* 2015;66:1934–41.
2. Sud K, Agarwal S, Parashar A, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. *Circulation.* 2016;133:1594–604.
3. Bertrand PB, Mihos CG, Yucel E. Mitral annular calcification and calcific mitral stenosis: therapeutic challenges and considerations. *Curr Treat Options Cardiovasc Med.* 2019;21:19.
4. Pasca I, Dang P, Tyagi G, et al. Survival in patients with degenerative mitral stenosis: results from a large retrospective cohort study. *J Am Soc Echocardiogr.* 2016;29:461–9.
5. Akram MR, Chan T, McAuliffe S, et al. Non-rheumatic annular mitral stenosis: prevalence and characteristics. *Eur J Echocardiogr.* 2009;10:103–5.
6. Asselbergs FW, Mozaffarian D, Katz R, et al. Association of renal function with cardiac calcifications in older adults: the cardiovascular health study. *Nephrol Dial Transplant.* 2009;24:834–40.
7. Ix JH, Shlipak MG, Katz R, et al. Kidney function and aortic valve and mitral annular calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis.* 2007;50:412–20.
8. Jesri A, Braitman LE, Pressman GS. Severe mitral annular calcification predicts chronic kidney disease. *Int J Cardiol.* 2008;128:193–6.
9. Pressman GS, Agarwal A, Braitman LE, et al. Mitral annular calcium causing mitral stenosis. *Am J Cardiol.* 2010;105:389–91.
10. Rao AK, Djamali A, Korcarz CE, et al. Mitral annular calcification is associated with reduced left ventricular function and inflammation in patients with chronic kidney disease. *J Am Soc Echocardiogr.* 2008;21:747–50.
11. Tsutsui RS, Banerjee K, Kapadia S, et al. Natural history of mitral stenosis in patients with mitral annular calcification. *JACC Cardiovasc Imaging.* 2019;12:1105–7.
12. Reddy YNV, Murgo JP, Nishimura RA. Complexity of defining severe “stenosis” from mitral annular calcification. *Circulation.* 2019;140:523–5.
13. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr.* 2009;10:1–25.
14. Chu JW, Levine RA, Chua S, et al. Assessing mitral valve area and orifice geometry in calcific mitral stenosis: a new solution by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr.* 2008;21:1006–9.
15. Oktay AA, Gilliland YE, Lavie CJ, et al. Echocardiographic assessment of degenerative mitral stenosis: a diagnostic challenge of an emerging cardiac disease. *Curr Probl Cardiol.* 2017;42:71–100.
16. Mow R, Murthy K, Romero-Corral A, et al. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. *J Am Soc Echocardiogr.* 2013;26:1135–42.
17. Hussain ST, Idrees J, Brozzi NA, et al. Use of annulus washer after debridement: a new mitral valve replacement technique for patients with severe mitral annular calcification. *J Thorac Cardiovasc Surg.* 2013;145:1672–4.
18. Kato Y, Hattori K, Bito Y, et al. Simple supra-annular prosthesis insertion for dialysis patients with extensive mitral annular calcification. *J Heart Valve Dis.* 2011;20:180–3.
19. Lin PY, Kan CD, Luo CY, et al. Mitral valve replacement in the presence of massive posterior annular calcification. *J Card Surg.* 1999;14:266–9.
20. McEnany MT. Mitral valve replacement in the presence of severe valvular and annular calcification. *J Card Surg.* 1993;8:117–24.
21. Nataf P, Pavie A, Jault F, et al. Intraatrial insertion of a mitral prosthesis in a destroyed or calcified mitral annulus. *Ann Thorac Surg.* 1994;58:163–7.
22. Shapira Y, Weisenberg DE, Vaturi M, et al. The impact of intraoperative transesophageal echocardiography in infective endocarditis. *Isr Med Assoc J.* 2007;9:299–302.
23. Guerrero M, Urena M, Himbert D, et al. 1-Year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. *J Am Coll Cardiol.* 2018;71:1841–53.

7. MITRAL REGURGITATION

7.1. Acute MR

1. Horstkotte D, Schulte HD, Niehues R, et al. Diagnostic and therapeutic considerations in acute, severe mitral regurgitation: experience in 42 consecutive patients entering the intensive care unit with pulmonary edema. *J Heart Valve Dis.* 1993;2:512–22.
2. Yoran C, Yellin EL, Becker RM, et al. Mechanism of reduction of mitral regurgitation with vasodilator therapy. *Am J Cardiol.* 1979;43:773–7.
3. Nanjappa MC, Ananthakrishna R, Hemanna Setty SK, et al. Acute severe mitral regurgitation following balloon mitral valvotomy: echocardiographic features, operative findings, and outcome in 50 surgical cases. *Catheter Cardiovasc Interv.* 2013;81:603–8.
4. Watanabe N. Acute mitral regurgitation. *Heart.* 2019;105:671–7.

7.1.1. Diagnosis of Acute MR

1. Watanabe N. Acute mitral regurgitation. *Heart.* 2019;105:671–7.

7.1.2. Medical Therapy

1. Horstkotte D, Schulte HD, Niehues R, et al. Diagnostic and therapeutic considerations in acute, severe mitral regurgitation: experience in 42 consecutive patients entering the intensive care unit with pulmonary edema. *J Heart Valve Dis.* 1993;2:512–22.
2. Yoran C, Yellin EL, Becker RM, et al. Mechanism of reduction of mitral regurgitation with vasodilator therapy. *Am J Cardiol.* 1979;43:773–7.

7.1.3. Intervention

1. Nanjappa MC, Ananthakrishna R, Hemanna Setty SK, et al. Acute severe mitral regurgitation following balloon mitral valvotomy: echocardiographic features, operative findings, and outcome in 50 surgical cases. *Catheter Cardiovasc Interv.* 2013;81:603–8.
2. Ternus BW, Mankad S, Edwards WD, et al. Clinical presentation and echocardiographic diagnosis of postinfarction papillary muscle rupture: A review of 22 cases. *Echocardiography.* 2017;34:973–7.
3. Leitman M, Tyomkin V, Raanani E, et al. Assessment and Management of Acute Severe Mitral Regurgitation in the Intensive Care Unit. *J Heart Valve Dis.* 2017;26:161–8.
4. Pasquier M, Sierro C, Yersin B, et al. Traumatic mitral valve injury after blunt chest trauma: a case report and review of the literature. *J Trauma.* 2010;68:243–6.
5. Pillai AA, Balasubramanian VR, Munuswamy H, et al. Acute severe mitral regurgitation with cardiogenic shock following balloon mitral valvuloplasty: echocardiographic findings and outcomes following surgery. *Cardiovasc Interv Ther.* 2019;34:260–8.

7.2. Chronic Primary MR

7.2.2. Diagnosis and Follow-Up of Chronic Primary MR

7.2.2.1. Diagnostic Testing: Initial Diagnosis

1. Bargiggia GS, Tronconi L, Sahn DJ, et al. A new method for quantitation of mitral regurgitation based on color flow Doppler imaging of flow convergence proximal to regurgitant orifice. *Circulation.* 1991;84:1481–9.
2. Recusani F, Bargiggia GS, Yoganathan AP, et al. A new method for quantification of regurgitant flow rate using color Doppler flow imaging of the flow convergence region proximal to a discrete orifice. An in vitro study. *Circulation.* 1991;83:594–604.
3. Tribouilloy C, Shen WF, Quere JP, et al. Assessment of severity of mitral regurgitation by measuring regurgitant jet width at its origin with transesophageal Doppler color flow imaging. *Circulation.* 1992;85:1248–53.
4. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: a long-term follow-up multicenter study. *J Am Coll Cardiol.* 2009;54:1961–8.
5. Enriquez-Sarano M, Avierinos J-F, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med.* 2005;352:875–83.
6. Ozdogan O, Yuksel A, Gurgun C, et al. Evaluation of the severity of mitral regurgitation by the use of signal void in magnetic resonance imaging. *Echocardiography.* 2009;26:1127–35.

7. Pflugfelder PW, Sechtem UP, White RD, et al. Noninvasive evaluation of mitral regurgitation by analysis of left atrial signal loss in cine magnetic resonance. *Am Heart J*. 1989;117:1113–9.
8. Myerson SG, d'Arcy J, Christiansen JP, et al. Determination of clinical outcome in mitral regurgitation with cardiovascular magnetic resonance quantification. *Circulation*. 2016;133:2287–96.
9. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303–71.
10. Dahm M, Iversen S, Schmid FX, et al. Intraoperative evaluation of reconstruction of the atrioventricular valves by transesophageal echocardiography. *Thorac Cardiovasc Surg*. 1987;35(Spec No. 2):140–2.
11. Saiki Y, Kasegawa H, Kawase M, et al. Intraoperative TEE during mitral valve repair: does it predict early and late postoperative mitral valve dysfunction? *Ann Thorac Surg*. 1998;66:1277–81.
12. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11:307–32.
13. Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med*. 1997;337:32–41.
14. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation*. 1999;99:400–5.
15. Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? *Ann Thorac Surg*. 2010;90:481–8.
16. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994;90:830–7.
17. Schuler G, Peterson KL, Johnson A, et al. Temporal response of left ventricular performance to mitral valve surgery. *Circulation*. 1979;59:1218–31.
18. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18:1301–10.
19. Jenner J, Sörensson P, Pernow J, et al. Contrast enhancement and image quality influence two- and three-dimensional echocardiographic determination of left ventricular volumes: comparison with magnetic resonance imaging. *Clin Med Insights Cardiol*. 2019;13:1179546819831980.
20. Tribouilloy C, Rusinaru D, Szymanski C, et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. *Eur J Echocardiogr*. 2011;12:702–10.
21. Suri RM, Clavel M-A, Schaff HV, et al. Effect of recurrent mitral regurgitation following degenerative mitral valve repair: long-term analysis of competing outcomes. *J Am Coll Cardiol*. 2016;67:488–98.
22. Bax JJ, Debonnaire P, Lancellotti P, et al. Transcatheter interventions for mitral regurgitation: multimodality imaging for patient selection and procedural guidance. *JACC Cardiovasc Imaging*. 2019;12:2029–48.
23. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2019;32:431–75.
24. Ghoreishi M, Evans CF, DeFilippi CR, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. *J Thorac Cardiovasc Surg*. 2011;142:1439–52.
25. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994;90:830–7.
26. Kang D-H, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation*. 2009;119:797–804.
27. Bonow RO. Chronic mitral regurgitation and aortic regurgitation: have indications for surgery changed? *J Am Coll Cardiol*. 2013;61:693–701.
28. Enriquez-Sarano M, Avierinos J-F, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875–83.
29. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238–44.
30. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets: a multicenter European study. *JACC Cardiovasc Imaging*. 2008;1:133–41.
31. Kang D-H, Park S-J, Sun BJ, et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. *J Am Coll Cardiol*. 2014;63:2398–407.
32. Rosen SE, Borer JS, Hochreiter C, et al. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. *Am J Cardiol*. 1994;74:374–80.
33. Quiñones MA, Douglas PS, Foster E, et al. American College of Cardiology/American Heart Association clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians—American Society of Internal Medicine Task Force on Clinical Competence. Developed in collaboration with the American Society of Echocardiography, the Society of Cardiovascular Anesthesiologists, and the Society of Pediatric Echocardiography. *Circulation*. 2003;107:1068–89.
34. Detaint D, Messika-Zeitoun D, Avierinos J-F, et al. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. *Circulation*. 2005;111:2391–7.
35. Sutton TM, Stewart RAH, Gerber IL, et al. Plasma natriuretic peptide levels increase with symptoms and severity of mitral regurgitation. *J Am Coll Cardiol*. 2003;41:2280–7.
36. Pizarro R, Bazzano OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *J Am Coll Cardiol*. 2009;54:1099–106.
37. Alashi A, Mentias A, Patel K, et al. Synergistic utility of brain natriuretic peptide and left ventricular global longitudinal strain in asymptomatic patients with significant primary mitral regurgitation and preserved systolic function undergoing mitral valve surgery. *Circ Cardiovasc Imaging*. 2016;9:e004451.
38. Klaar U, Gabriel H, Bergler-Klein J, et al. Prognostic value of serial B-type natriuretic peptide measurement in asymptomatic organic mitral regurgitation. *Eur J Heart Fail*. 2011;13:163–9.
39. Mentias A, Patel K, Patel H, et al. Prognostic utility of brain natriuretic peptide in asymptomatic patients with significant mitral regurgitation and preserved left ventricular ejection fraction. *Am J Cardiol*. 2016;117:258–63.
40. Magne J, Mahjoub H, Pierard LA, et al. Prognostic importance of brain natriuretic peptide and left ventricular longitudinal function in asymptomatic degenerative mitral regurgitation. *Heart*. 2012;98:584–91.
41. Hiemstra YL, Tomsic A, van Wijngaarden SE, et al. Prognostic value of global longitudinal strain and etiology after surgery for primary mitral regurgitation. *JACC Cardiovasc Imaging*. 2020;13:577–85.
42. Clavel M-A, Tribouilloy C, Vanoverschelde J-L, et al. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol*. 2016;68:1297–307.
43. Kim HM, Cho G-Y, Hwang I-C, et al. Myocardial strain in prediction of outcomes after surgery for severe mitral regurgitation. *JACC Cardiovasc Imaging*. 2018;11:1235–44.

7.2.2.2. Diagnostic Testing: Changing Signs or Symptoms

1. Antoine C, Benfari G, Michelena HI, et al. Clinical outcome of degenerative mitral regurgitation: critical importance of echocardiographic quantitative assessment in routine practice. *Circulation*. 2018;138:1317–26.
2. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation*. 1999;99:400–5.

7.2.2.3. Diagnostic Testing: Routine Follow-Up

1. Zilberszac R, Heinze G, Binder T, et al. Long-term outcome of active surveillance in severe but asymptomatic primary mitral regurgitation. *JACC Cardiovasc Imaging*. 2018;11:1213–21.

7.2.2.4. Diagnostic Testing: Cardiac Catheterization

1. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation*. 2012;125:2138–50.

7.2.2.5. Diagnostic Testing: Exercise Testing

1. Tischler MD, Battle RW, Ashikaga T, et al. Effects of exercise on left ventricular performance determined by echocardiography in chronic, severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol*. 1996;77:397–402.
2. Tischler MD, Battle RW, Saha M, et al. Observations suggesting a high incidence of exercise-induced severe mitral regurgitation in patients with mild rheumatic mitral valve disease at rest. *J Am Coll Cardiol*. 1995;25:128–33.
3. Magne J, Lancellotti P, Piérard LA. Exercise-induced changes in degenerative mitral regurgitation. *J Am Coll Cardiol*. 2010;56:300–9.
4. Magne J, Lancellotti P, Piérard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. *Circulation*. 2010;122:33–41.

7.2.3. Medical Therapy

1. Ahmed MI, Aban I, Lloyd SG, et al. A randomized controlled phase IIb trial of beta(1)-receptor blockade for chronic degenerative mitral regurgitation. *J Am Coll Cardiol*. 2012;60:833–8.
2. Nemoto S, Hamawaki M, De Freitas G, et al. Differential effects of the angiotensin-converting enzyme inhibitor lisinopril versus the beta-adrenergic receptor blocker atenolol on hemodynamics and left ventricular contractile function in experimental mitral regurgitation. *J Am Coll Cardiol*. 2002;40:149–54.
3. Varadarajan P, Joshi N, Appel D, et al. Effect of beta-blocker therapy on survival in patients with severe mitral regurgitation and normal left ventricular ejection fraction. *Am J Cardiol*. 2008;102:611–5.
4. Dujardin KS, Enriquez-Sarano M, Bailey KR, et al. Effect of losartan on degree of mitral regurgitation quantified by echocardiography. *Am J Cardiol*. 2001;87:570–6.
5. Harris KM, Aeppli DM, Carey CF. Effects of angiotensin-converting enzyme inhibition on mitral regurgitation severity, left ventricular size, and functional capacity. *Am Heart J*. 2005;150:1106.
6. Kizilbash AM, Willett DL, Brickner ME, et al. Effects of afterload reduction on vena contracta width in mitral regurgitation. *J Am Coll Cardiol*. 1998;32:427–31.
7. Tischler MD, Rowan M, LeWinter MM. Effect of enalapril therapy on left ventricular mass and volumes in asymptomatic chronic, severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol*. 1998;82:242–5.
8. Wisenbaugh T, Sinovich V, Dullabh A, et al. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral and isolated aortic regurgitation. *J Heart Valve Dis*. 1994;3:197–204.

7.2.4. Intervention

1. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation*. 1999;99:400–5.
2. Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? *Ann Thorac Surg*. 2010;90:481–8.
3. Rosenhek R, Rader F, Klačar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238–44.
4. Kang D-H, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation*. 2009;119:797–804.
5. Schuler G, Peterson KL, Johnson A, et al. Temporal response of left ventricular performance to mitral valve surgery. *Circulation*. 1979;59:1218–31.
6. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994;90:830–7.
7. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: a long-term follow-up multicenter study. *J Am Coll Cardiol*. 2009;54:1961–8.
8. Enriquez-Sarano M, Avierinos J-F, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875–83.
9. Crawford MH, Soucek J, Orian CA, et al. Determinants of survival and left ventricular performance after mitral valve replacement. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. *Circulation*. 1990;81:1173–81.

10. Borow KM, Green LH, Mann T, et al. End-systolic volume as a predictor of postoperative left ventricular performance in volume overload from valvular regurgitation. *Am J Med*. 1980;68:655–63.
11. Suri RM, Clavel M-A, Schaff HV, et al. Effect of recurrent mitral regurgitation following degenerative mitral valve repair: long-term analysis of competing outcomes. *J Am Coll Cardiol*. 2016;67:488–98.
12. Vassileva CM, Mishkel G, McNeely C, et al. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation*. 2013;127:1870–6.
13. Suri RM, Vanoverschelde J-L, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA*. 2013;310:609–16.
14. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets: a multicenter European study. *JACC Cardiovasc Imaging*. 2008;1:133–41.
15. Lazam S, Vanoverschelde J-L, Tribouilloy C, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. *Circulation*. 2017;135:410–22.
16. Tribouilloy C, Rusinaru D, Szymanski C, et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. *Eur J Echocardiogr*. 2011;12:702–10.
17. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844–54.
18. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–406.
19. Dillon J, Yakub MA, Kong PK, et al. Comparative long-term results of mitral valve repair in adults with chronic rheumatic disease and degenerative disease: is repair for “burnt-out” rheumatic disease still inferior to repair for degenerative disease in the current era? *J Thorac Cardiovasc Surg*. 2015;149:771–7.
20. Gillinov AM, Blackstone EH, Alaulaqi A, et al. Outcomes after repair of the anterior mitral leaflet for degenerative disease. *Ann Thorac Surg*. 2008;86:708–17.
21. Weiner MM, Hofer I, Lin H-M, et al. Relationship among surgical volume, repair quality, and perioperative outcomes for repair of mitral insufficiency in a mitral valve reference center. *J Thorac Cardiovasc Surg*. 2014;148:2021–6.
22. Enriquez-Sarano M, Suri RM, Clavel M-A, et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. *J Thorac Cardiovasc Surg*. 2015;150:50–8.
23. David TE, Ivanov J, Armstrong S, et al. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg*. 2005;130:1242–9.
24. Suri RM, Schaff HV, Dearani JA, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. *Ann Thorac Surg*. 2006;82:819–26.
25. Castillo JG, Anyanwu AC, El-Eshmawi A, et al. All anterior and bileaflet mitral valve prolapses are repairable in the modern era of reconstructive surgery. *Eur J Cardiothorac Surg*. 2014;45:139–45.
26. Chikwe J, Toyoda N, Anyanwu AC, et al. Relation of mitral valve surgery volume to repair rate, durability, and survival. *J Am Coll Cardiol*. 2017;69:2397–406.
27. Castillo JG, Anyanwu AC, Fuster V, et al. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. *J Thorac Cardiovasc Surg*. 2012;144:308–12.
28. El-Eshmawi A, Castillo JG, Tang GHL, et al. Developing a mitral valve center of excellence. *Curr Opin Cardiol*. 2018;33:155–61.
29. Bonow RO, Adams DH. The time has come to define centers of excellence in mitral valve repair. *J Am Coll Cardiol*. 2016;67:499–501.
30. Badhwar V, Peterson ED, Jacobs JP, et al. Longitudinal outcome of isolated mitral repair in older patients: results from 14,604 procedures performed from 1991 to 2007. *Ann Thorac Surg*. 2012;94:1870–7.
31. Chikwe J, Goldstone AB, Passage J, et al. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J*. 2011;32:618–26.
32. Starling MR. Effects of valve surgery on left ventricular contractile function in patients with long-term mitral regurgitation. *Circulation*. 1995;92:811–8.
33. McClure RS, Athanasopoulos LV, McGurk S, et al. One thousand minimally invasive mitral valve operations: early outcomes, late outcomes, and echocardiographic follow-up. *J Thorac Cardiovasc Surg*. 2013;145:1199–206.

34. Arcidi JM Jr, Rodriguez E, Elbeery JR, et al. Fifteen-year experience with minimally invasive approach for reoperations involving the mitral valve. *J Thorac Cardiovasc Surg*. 2012;143:1062–8.
35. Holzhey DM, Seeburger J, Misfeld M, et al. Learning minimally invasive mitral valve surgery: a cumulative sum sequential probability analysis of 3895 operations from a single high-volume center. *Circulation*. 2013;128:483–91.
36. Mihaljevic T, Jarrett CM, Gillinov AM, et al. Robotic repair of posterior mitral valve prolapse versus conventional approaches: potential realized. *J Thorac Cardiovasc Surg*. 2011;141:72–80.e1–4.
37. Suri RM, Burkhart HM, Daly RC, et al. Robotic mitral valve repair for all prolapse subsets using techniques identical to open valvuloplasty: establishing the benchmark against which percutaneous interventions should be judged. *J Thorac Cardiovasc Surg*. 2011;142:970–9.
38. Suri RM, Schaff HV, Meyer SR, et al. Thoracoscopic versus open mitral valve repair: a propensity score analysis of early outcomes. *Ann Thorac Surg*. 2009;88:1185–90.
39. David TE, Armstrong S, McCrindle BW, et al. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation*. 2013;127:1485–92.
40. David TE, David CM, Tsang W, et al. Long-term results of mitral valve repair for regurgitation due to leaflet prolapse. *J Am Coll Cardiol*. 2019;74:1044–53.
41. Quintana E, Suri RM, Thalji NM, et al. Left ventricular dysfunction after mitral valve repair—the fallacy of “normal” preoperative myocardial function. *J Thorac Cardiovasc Surg*. 2014;148:2752–60.
42. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT registry report. *J Am Coll Cardiol*. 2017;70:2315–27.
43. Yankah CA, Siniawski H, Detschades C, et al. Rheumatic mitral valve repair: 22-year clinical results. *J Heart Valve Dis*. 2011;20:257–64.
44. Mauri L, Foster E, Glower DD, et al. 4-Year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol*. 2013;62:317–28.
45. Bax JJ, Debonnaire P, Lancellotti P, et al. Transcatheter interventions for mitral regurgitation: multimodality imaging for patient selection and procedural guidance. *JACC Cardiovasc Imaging*. 2019;12:2029–48.
46. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2019;32:431–75.
47. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–406.
48. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844–54.
49. Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST II. *J Am Soc Echocardiogr*. 2007;20:1131–40.
50. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011–2012 Pilot European Sentinel Registry. *J Am Coll Cardiol*. 2014;64:875–84.
51. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT registry report. *J Am Coll Cardiol*. 2017;70:2315–27.
52. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374:1511–20.
53. Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med*. 2019;381:739–48.
54. Ji Q, Zhao Y, Shen J, et al. Predictors of ischemic mitral regurgitation improvement after surgical revascularization plus mitral valve repair for moderate ischemic mitral regurgitation. *J Card Surg*. 2020;35:528–35.
55. Kopjar T, Gasparovic H, Mestres CA, et al. Meta-analysis of concomitant mitral valve repair and coronary artery bypass surgery versus isolated coronary artery bypass surgery in patients with moderate ischaemic mitral regurgitation. *Eur J Cardiothorac Surg*. 2016;50:212–22.
56. Virk SA, Tian DH, Sriravindrarajah A, et al. Mitral valve surgery and coronary artery bypass grafting for moderate-to-severe ischemic mitral regurgitation: meta-analysis of clinical and echocardiographic outcomes. *J Thorac Cardiovasc Surg*. 2017;154:127–36.

7.3. Chronic Secondary MR

7.3.1. Stages of Chronic Secondary MR

1. Uretsky S, Gillam L, Lang R, et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. *J Am Coll Cardiol*. 2015;65:1078–88.
2. Grayburn PA, Carabello B, Hung J, et al. Defining “severe” secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64:2792–801.
3. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23–32.
4. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med*. 2016;374:344–53.
5. Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2016;374:1932–41.
6. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178–88.

7.3.2. Diagnosis of Chronic Secondary MR

1. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303–71.
2. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103:1759–64.
3. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–18.
4. Tommaso CL, Fullerton DA, Feldman T, et al. SCAI/AATS/ACC/STS operator and institutional requirements for transcatheter valve repair and replacement. Part II. mitral valve. *J Am Coll Cardiol*. 2014;64:1515–26.
5. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol*. 2013;62:1052–61.

7.3.3. Medical Therapy

1. SOLVD Investigators, Yusuf S, Pitt B, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685–91.
2. Eriksson SV, Eneroth P, Kjekshus J, et al. Neuroendocrine activation in relation to left ventricular function in chronic severe congestive heart failure: a subgroup analysis from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Clin Cardiol*. 1994;17:603–6.
3. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362:772–6.
4. Krum H, Roecker EB, Mohaci P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA*. 2003;289:712–8.
5. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–17.
6. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107:1985–90.
7. van Bommel RJ, Marsan NA, Delgado V, et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. *Circulation*. 2011;124:912–9.
8. Krag D-H, Park S-J, Shin S-H, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation*. 2019;139:1354–65.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of

Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–327.

10. Mullens W, Martens P. Sacubitril/Valsartan to reduce secondary mitral regurgitation. *Circulation*. 2019;139:1366–70.
11. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–53.
12. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–18.

7.3.4. Intervention

1. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–18.
2. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–306.
3. Ailawadi G, Lim DS, Mack MJ, et al. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation*. 2019;139:37–47.
4. Arnold SV, Chinnakondepalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. *J Am Coll Cardiol*. 2019;73:2123–32.
5. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging*. 2019;12:353–62.
6. Nishimura RA, Bonow RO. Percutaneous repair of secondary mitral regurgitation—a tale of two trials. *N Engl J Med*. 2018;379:2374–6.
7. Swaans MJ, Bakker ALM, Alipour A, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. *JACC Cardiovasc Interv*. 2014;7:875–81.
8. Auricchio A, Schillinger W, Meyer S, et al. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. *J Am Coll Cardiol*. 2011;58:2183–9.
9. Deja MA, Grayburn PA, Sun B, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation*. 2012;125:2639–48.
10. Di Mauro M, Di Giammarco G, Vitolla G, et al. Impact of no-to-moderate mitral regurgitation on late results after isolated coronary artery bypass grafting in patients with ischemic cardiomyopathy. *Ann Thorac Surg*. 2006;81:2128–34.
11. Bax JJ, Braun J, Somer ST, et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation*. 2004;110:II103–8.
12. Fattouch K, Guccione F, Sampognaro R, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. *J Thorac Cardiovasc Surg*. 2009;138:278–85.
13. Samad Z, Shaw LK, Phelan M, et al. Management and outcomes in patients with moderate or severe functional mitral regurgitation and severe left ventricular dysfunction. *Eur Heart J*. 2015;36:2733–41.
14. Nishimura RA, Vahanian A, Eleid MF, et al. Mitral valve disease—current management and future challenges. *Lancet*. 2016;387:1324–34.
15. Deja MA, Grayburn PA, Sun B, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation*. 2012;125:2639–48.
16. Rankin JS, Grau-Sepulveda M, Shahian DM, et al. The impact of mitral disease etiology on operative mortality after mitral valve operations. *Ann Thorac Surg*. 2018;106:1406–13.
17. Gammie JS, Chikwe J, Badhwar V, et al. Isolated mitral valve surgery: the Society of Thoracic Surgeons Adult Cardiac Surgery Database analysis. *Ann Thorac Surg*. 2018;106:716–27.
18. Kihara T, Gillinov AM, Takasaki K, et al. Mitral regurgitation associated with mitral annular dilation in patients with lone atrial fibrillation: an echocardiographic study. *Echocardiography*. 2009;26:885–9.
19. Vohra HA, Whistance RN, Magan A, et al. Mitral valve repair for severe mitral regurgitation secondary to lone atrial fibrillation. *Eur J Cardiothorac Surg*. 2012;42:634–7.
20. Takahashi Y, Abe Y, Sasaki Y, et al. Mitral valve repair for atrial functional mitral regurgitation in patients with chronic atrial fibrillation. *Interact Cardiovasc Thorac Surg*. 2015;21:163–8.
21. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med*. 2016;374:344–53.
22. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2005;45:381–7.

23. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103:1759–64.
24. Lancellotti P, Gérard PL, Piérard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. *Eur Heart J*. 2005;26:1528–32.
25. Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol*. 2003;91:538–43.
26. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart*. 2011;97:1675–80.
27. Mihajlovic T, Lam B-K, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol*. 2007;49:2191–201.
28. Harris KM, Sundt TM 3rd, Aeppli D, et al. Can late survival of patients with moderate ischemic mitral regurgitation be impacted by intervention on the valve? *Ann Thorac Surg*. 2002;74:1468–75.
29. Benedetto U, Melina G, Roscitano A, et al. Does combined mitral valve surgery improve survival when compared to revascularization alone in patients with ischemic mitral regurgitation? A meta-analysis on 2479 patients. *J Cardiovasc Med (Hagerstown)*. 2009;10:109–14.
30. Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg*. 1995;9:568–74.
31. Chan KMJ, Punjabi PP, Flather M, et al. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. *Circulation*. 2012;126:2502–10.
32. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23–32.
33. Sugimoto T, Okada M, Ozaki N, et al. Long-term evaluation of treatment for functional tricuspid regurgitation with regurgitant volume: characteristic differences based on primary cardiac lesion. *J Thorac Cardiovasc Surg*. 1999;117:463–71.
34. Fukuda S, Gillinov AM, McCarthy PM, et al. Determinants of recurrent or residual functional tricuspid regurgitation after tricuspid annuloplasty. *Circulation*. 2006;114:I582–7.
35. Ling LF, Obuchowski NA, Rodriguez L, et al. Accuracy and interobserver concordance of echocardiographic assessment of right ventricular size and systolic function: a quality control exercise. *J Am Soc Echocardiogr*. 2012;25:709–13.
36. Rudski LG, Lai WW, Afila J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.
37. Beygui F, Furber A, Delépine S, et al. Routine breath-hold gradient echo MRI-derived right ventricular mass, volumes and function: accuracy, reproducibility and coherence study. *Int J Cardiovasc Imaging*. 2004;20:509–16.
38. Caudron J, Fares J, Vivier P-H, et al. Diagnostic accuracy and variability of three semi-quantitative methods for assessing right ventricular systolic function from cardiac MRI in patients with acquired heart disease. *Eur Radiol*. 2011;21:2111–20.
39. Maceira AM, Prasad SK, Khan M, et al. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *Eur Heart J*. 2006;27:2879–88.
40. Navia JL, Brozzi NA, Klein AL, et al. Moderate tricuspid regurgitation with left-sided degenerative heart valve disease: to repair or not to repair? *Ann Thorac Surg*. 2012;93:59–67.
41. Nesser HJ, Tkalec W, Patel AR, et al. Quantitation of right ventricular volumes and ejection fraction by three-dimensional echocardiography in patients: comparison with magnetic resonance imaging and radionuclide ventriculography. *Echocardiography*. 2006;23:666–80.
42. Pavlicek M, Wahl A, Rutz T, et al. Right ventricular systolic function assessment: rank of echocardiographic methods vs. cardiac magnetic resonance imaging. *Eur J Echocardiogr*. 2011;12:871–80.
43. Speiser U, Hirschberger M, Pilz G, et al. Tricuspid annular plane systolic excursion assessed using MRI for semi-quantification of right ventricular ejection fraction. *Br J Radiol*. 2012;85:e716–21.
44. Magne J, Gierd N, Sénéchal M, et al. Mitral repair versus replacement for ischemic mitral regurgitation: comparison of short-term and long-term survival. *Circulation*. 2009;120:S104–11.

45. Lorusso R, Gelsomino S, Vizzardi E, et al. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian Study on the Treatment of Ischemic Mitral Regurgitation (ISTIMIR). *J Thorac Cardiovasc Surg.* 2013;145:128–39.
46. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2004;128:916–24.
47. Miller DC. Ischemic mitral regurgitation redux—to repair or to replace? *J Thorac Cardiovasc Surg.* 2001;122:1059–62.
48. Grayburn PA, Foster E, Sangli C, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. *Circulation.* 2013;128:1667–74.
49. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging.* 2019;20:620–4.
50. Braun J, Bax JJ, Versteegh MI, et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg.* 2005;27:847–53.
51. Kim D-H, Heo R, Handschumacher MD, et al. Mitral valve adaptation to isolated annular dilation: insights into the mechanism of atrial functional mitral regurgitation. *JACC Cardiovasc Imaging.* 2019;12:665–77.
52. Deferm S, Bertrand PB, Verbrugge FH, et al. Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol.* 2019;73:2465–76.
53. Gertz ZM, Raina A, Saghy L, et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol.* 2011;58:1474–81.

8. TRICUSPID VALVE DISEASE

8.1. Classification and Stages of TR

1. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol.* 2004;43:405–9.
2. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging.* 2014;7:1185–94.
3. Lee J-W, Song J-M, Park JP, et al. Long-term prognosis of isolated significant tricuspid regurgitation. *Circ J.* 2010;74:375–80.
4. Bar N, Schwartz LA, Biner S, et al. Clinical outcome of isolated tricuspid regurgitation in patients with preserved left ventricular ejection fraction and pulmonary hypertension. *J Am Soc Echocardiogr.* 2018;31:34–41.
5. Benfari G, Antoine C, Miller WL, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation.* 2019;140:196–206.
6. Wang N, Fulcher J, Abeyuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J.* 2019;40:476–84.
7. Chorin E, Rozenbaum Z, Topilsky Y, et al. Tricuspid regurgitation and long-term clinical outcomes. *Eur Heart J Cardiovasc Imaging.* 2020;21:157–65.
8. Lin G, Nishimura RA, Connolly HM, et al. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J Am Coll Cardiol.* 2005;45:1672–5.
9. Chang JD, Manning WJ, Ebrille E, et al. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. *J Am Coll Cardiol.* 2017;69:2331–41.
10. Paniagua D, Aldrich HR, Lieberman EH, et al. Increased prevalence of significant tricuspid regurgitation in patients with transvenous pacemakers leads. *Am J Cardiol.* 1998;82:1130–2, A9.
11. Park SJ, Gentry JL 3rd, Varma N, et al. Transvenous extraction of pacemaker and defibrillator leads and the risk of tricuspid valve regurgitation. *JACC Clin Electrophysiol.* 2018;4:1421–8.
12. Mediratta A, Addetia K, Yamat M, et al. 3D Echocardiographic location of implantable device leads and mechanism of associated tricuspid regurgitation. *JACC Cardiovasc Imaging.* 2014;7:337–47.
13. Addetia K, Harb SC, Hahn RT, et al. Cardiac implantable electronic device lead-induced tricuspid regurgitation. *JACC Cardiovasc Imaging.* 2019;12:622–36.
14. Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging.* 2012;5:314–23.
15. Mutlak D, Lessick J, Reisner SA, et al. Echocardiography-based spectrum of severe tricuspid regurgitation: the frequency of apparently idiopathic tricuspid regurgitation. *J Am Soc Echocardiogr.* 2007;20:405–8.
16. Zhao SX, Soltanzad N, Swaminathan A, et al. Frequency and associated clinical features of functional tricuspid regurgitation in patients with chronic atrial fibrillation. *Am J Cardiol.* 2017;119:1371–7.
17. Utsunomiya H, Itabashi Y, Mihara H, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. *Circ Cardiovasc Imaging.* 2017;10:e004897.
18. Yamasaki N, Kondo F, Kubo T, et al. Severe tricuspid regurgitation in the aged: atrial remodeling associated with long-standing atrial fibrillation. *J Cardiol.* 2006;48:315–23.
19. Maeder MT, Holst DP, Kaye DM. Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. *J Card Fail.* 2008;14:824–30.
20. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol.* 2002;90:1405–9.
21. Mangoni AA, DiSalvo TG, Vlahakes GJ, et al. Outcome following isolated tricuspid valve replacement. *Eur J Cardiothorac Surg.* 2001;19:68–73.
22. Kim JB, Jung S-H, Choo SJ, et al. Surgical outcomes of severe tricuspid regurgitation: predictors of adverse clinical outcomes. *Heart.* 2013;99:181–7.
23. Ailawadi G, Lapar DJ, Swenson BR, et al. Model for end-stage liver disease predicts mortality for tricuspid valve surgery. *Ann Thorac Surg.* 2009;87:1460–7.

8.2. Tricuspid Regurgitation

8.2.1. Diagnosis of TR

1. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30:303–71.
2. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr.* 2010;11:307–32.
3. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. *Circulation.* 2012;125:2138–50.
4. Hahn RT. Finding concordance in discord: the value of discordant invasive and echocardiographic pulmonary artery pressure measurements with severe tricuspid regurgitation. *Eur Heart J.* 2020;41:2796–8.
5. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J.* 2020;41:2785–95.
6. Hahn RT, Thomas JD, Khalique OK, et al. Imaging assessment of tricuspid regurgitation severity. *JACC Cardiovasc Imaging.* 2019;12:469–90.
7. Dahou A, Ong G, Hamid N, et al. Quantifying tricuspid regurgitation severity: a comparison of proximal isovelocity surface area and novel quantitative Doppler methods. *JACC Cardiovasc Imaging.* 2019;12:560–2.
8. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging.* 2017;18:1342–3.
9. Peri Y, Sadeh B, Sherez C, et al. Quantitative assessment of effective regurgitant orifice: impact on risk stratification, and cut-off for severe and torrential tricuspid regurgitation grade. *Eur Heart J Cardiovasc Imaging.* 2019;21:768–76.
10. Utsunomiya H, Harada Y, Susawa H, et al. Comprehensive evaluation of tricuspid regurgitation location and severity using vena contracta analysis: a color Doppler three-dimensional transesophageal echocardiographic study. *J Am Soc Echocardiogr.* 2019;32:1526–37.e2.
11. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.
12. Chopra HK, Nanda NC, Fan P, et al. Can two-dimensional echocardiography and Doppler color flow mapping identify the need for tricuspid valve repair? *J Am Coll Cardiol.* 1989;14:1266–74.
13. Dreyfus GD, Corbi PJ, Chan KMJ, et al. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg.* 2005;79:127–32.
14. Lancellotti P, Tribouilloy C, Hagendorff A, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr.* 2010;11:223–44.
15. Sugimoto T, Okada M, Ozaki N, et al. Long-term evaluation of treatment for functional tricuspid regurgitation with regurgitant volume:

characteristic differences based on primary cardiac lesion. *J Thorac Cardiovasc Surg.* 1999;117:463–71.

16. Ling LF, Obuchowski NA, Rodriguez L, et al. Accuracy and interobserver concordance of echocardiographic assessment of right ventricular size and systolic function: a quality control exercise. *J Am Soc Echocardiogr.* 2012;25:709–13.
17. Rudski LG, Lai WW, Afila J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23:685–713.

8.2.2. Medical Therapy

1. Antoniou T, Koletsis EN, Prokakis C, et al. Hemodynamic effects of combination therapy with inhaled nitric oxide and iloprost in patients with pulmonary hypertension and right ventricular dysfunction after high-risk cardiac surgery. *J Cardiothorac Vasc Anesth.* 2013;27:459–66.
2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol.* 2009;53:1573–619.
3. Wang J, Han J, Li Y, et al. Impact of surgical ablation of atrial fibrillation on the progression of tricuspid regurgitation and right-sided heart remodeling after mitral-valve surgery: a propensity-score matching analysis. *J Am Heart Assoc.* 2016;5:e004213.
4. Stulak JM, Schaff HV, Dearani JA, et al. Restoration of sinus rhythm by the Maze procedure halts progression of tricuspid regurgitation after mitral surgery. *Ann Thorac Surg.* 2008;86:40–4; discussion 44–5.

8.2.3. Timing of Intervention

1. Staab ME, Nishimura RA, Dearani JA. Isolated tricuspid valve surgery for severe tricuspid regurgitation following prior left heart valve surgery: analysis of outcome in 34 patients. *J Heart Valve Dis.* 1999;8:567–74.
2. Vassileva CM, Shabosky J, Boley T, et al. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg.* 2012;143:1043–9.
3. Dreyfus GD, Corbi PJ, Chan KMJ, et al. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg.* 2005;79:127–32.
4. Navia JL, Brozzi NA, Klein AL, et al. Moderate tricuspid regurgitation with left-sided degenerative heart valve disease: to repair or not to repair? *Ann Thorac Surg.* 2012;93:59–67.
5. Benedetto U, Melina G, Angeloni E, et al. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. *J Thorac Cardiovasc Surg.* 2012;143:632–8.
6. Van de Veire NR, Braun J, Delgado V, et al. Tricuspid annuloplasty prevents right ventricular dilatation and progression of tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. *J Thorac Cardiovasc Surg.* 2011;141:1431–9.
7. Calafiore AM, Gallina S, Iacò AL, et al. Mitral valve surgery for functional mitral regurgitation: should moderate-or-more tricuspid regurgitation be treated? A propensity score analysis. *Ann Thorac Surg.* 2009;87:698–703.
8. Chan V, Burwash IG, Lam B-K, et al. Clinical and echocardiographic impact of functional tricuspid regurgitation repair at the time of mitral valve replacement. *Ann Thorac Surg.* 2009;88:1209–15.
9. Kim JB, Yoo DG, Kim GS, et al. Mild-to-moderate functional tricuspid regurgitation in patients undergoing valve replacement for rheumatic mitral disease: the influence of tricuspid valve repair on clinical and echocardiographic outcomes. *Heart.* 2012;98:24–30.
10. Yilmaz O, Suri RM, Dearani JA, et al. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. *J Thorac Cardiovasc Surg.* 2011;142:608–13.
11. Hamandi M, Smith RL, Ryan WH, et al. Outcomes of isolated tricuspid valve surgery have improved in the modern era. *Ann Thorac Surg.* 2019;108:11–5.
12. Kim Y-J, Kwon D-A, Kim H-K, et al. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. *Circulation.* 2009;120:1672–8.
13. Messika-Zeitoun D, Thomson H, Bellamy M, et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg.* 2004;128:296–302.
14. Møller JE, Pellikka PA, Bernheim AM, et al. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation.* 2005;112:3320–7.

15. Kadri AN, Menon V, Sammour YM, et al. Outcomes of patients with severe tricuspid regurgitation and congestive heart failure. *Heart.* 2019;105:1813–7.
16. Lee J-W, Song J-M, Park JP, et al. Long-term prognosis of isolated significant tricuspid regurgitation. *Circ J.* 2010;74:375–80.
17. Axtell AL, Bhambhani V, Moonsamy P, et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol.* 2019;74:715–25.
18. Pfannmüller B, Misfeld M, Borger MA, et al. Isolated reoperative minimally invasive tricuspid valve operations. *Ann Thorac Surg.* 2012;94:2005–10.
19. Kim JB, Jung S-H, Choo SJ, et al. Clinical and echocardiographic outcomes after surgery for severe isolated tricuspid regurgitation. *J Thorac Cardiovasc Surg.* 2013;146:278–84.
20. Mangoni AA, DiSalvo TG, Vlahakes GJ, et al. Outcome following isolated tricuspid valve replacement. *Eur J Cardiothorac Surg.* 2001;19:68–73.
21. Zack CJ, Fender EA, Chandrasekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol.* 2017;70:2953–60.
22. Topilsky Y, Khanna AD, Oh JK, et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. *Circulation.* 2011;123:1929–39.
23. Fender EA, Petrescu I, Ionescu F, et al. Prognostic importance and predictors of survival in isolated tricuspid regurgitation: a growing problem. *Mayo Clin Proc.* 2019;94:2032–9.
24. Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging.* 2012;5:314–23.
25. Mutlak D, Lessick J, Reisner SA, et al. Echocardiography-based spectrum of severe tricuspid regurgitation: the frequency of apparently idiopathic tricuspid regurgitation. *J Am Soc Echocardiogr.* 2007;20:405–8.
26. Taramasso M, Hahn RT, Alessandrini H, et al. The international multicenter TriValve registry: which patients are undergoing transcatheter tricuspid repair? *JACC Cardiovasc Interv.* 2017;10:1982–90.
27. Asmarats L, Puri R, Latib A, et al. Transcatheter tricuspid valve interventions: landscape, challenges, and future directions. *J Am Coll Cardiol.* 2018;71:2935–56.
28. Chikwe J, Anyanwu AC. Surgical strategies for functional tricuspid regurgitation. *Semin Thorac Cardiovasc Surg.* 2010;22:90–6.
29. Kwon D-A, Park J-S, Chang H-J, et al. Prediction of outcome in patients undergoing surgery for severe tricuspid regurgitation following mitral valve surgery and role of tricuspid annular systolic velocity. *Am J Cardiol.* 2006;98:659–61.
30. Lee R, Li S, Rankin JS, et al. Fifteen-year outcome trends for valve surgery in North America. *Ann Thorac Surg.* 2011;91:677–84.
31. Rogers JH, Bolling SF. The tricuspid valve: current perspective and evolving management of tricuspid regurgitation. *Circulation.* 2009;119:2718–25.
32. Kwak J-J, Kim Y-J, Kim M-K, et al. Development of tricuspid regurgitation late after left-sided valve surgery: a single-center experience with long-term echocardiographic examinations. *Am Heart J.* 2008;155:732–7.
33. Chopra HK, Nanda NC, Fan P, et al. Can two-dimensional echocardiography and Doppler color flow mapping identify the need for tricuspid valve repair? *J Am Coll Cardiol.* 1989;14:1266–74.
34. Mahesh B, Wells F, Nashef S, et al. Role of concomitant tricuspid surgery in moderate functional tricuspid regurgitation in patients undergoing left heart valve surgery. *Eur J Cardiothorac Surg.* 2013;43:2–8.
35. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol.* 2009;53:401–8.
36. Sagie A, Schwammenthal E, Padial LR, et al. Determinants of functional tricuspid regurgitation in incomplete tricuspid valve closure: Doppler color flow study of 109 patients. *J Am Coll Cardiol.* 1994;24:446–53.
37. Lin G, Nishimura RA, Connolly HM, et al. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J Am Coll Cardiol.* 2005;45:1672–5.
38. Alqahtani F, Berzinger CO, Aljohani S, et al. Contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. *J Am Heart Assoc.* 2017;6:e007597.
39. Jeganathan R, Armstrong S, Al-Alao B, et al. The risk and outcomes of reoperative tricuspid valve surgery. *Ann Thorac Surg.* 2013;95:119–24.

9. PULMONIC VALVE DISEASE

1. Stout KK, Daniels CJ, Aboulhosen JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the

American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e698–800.

10. MIXED VALVE DISEASE

10.1. Diagnosis of Mixed VHD

1. Unger P, Rosenhek R, Dedobbeleer C, et al. Management of multiple valve disease. *Heart*. 2011;97:272–7.
2. Lee R, Li S, Rankin JS, et al. Fifteen-year outcome trends for valve surgery in North America. *Ann Thorac Surg*. 2011;91:677–84.
3. Venneri L, Khattar RS, Senior R. Assessment of complex multi-valve disease and prosthetic valves. *Heart Lung Circ*. 2019;28:1436–46.
4. lung B, Delgado V, Rosenhek R, et al. Contemporary presentation and management of valvular heart disease: the EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation*. 2019;140:1156–69.
5. Unger P, Clavel MA, Lindman BR, et al. Pathophysiology and management of multivalvular disease. *Nat Rev Cardiol*. 2016;13:429–40.

10.2. Timing of Intervention for Mixed VHD

10.2.1. Intervention for Mixed AS and AR

1. Zilberszac R, Gabriel H, Schemper M, et al. Outcome of combined stenotic and regurgitant aortic valve disease. *J Am Coll Cardiol*. 2013;61:1489–95.
2. Egbe AC, Luis SA, Padang R, et al. Outcomes in moderate mixed aortic valve disease: is it time for a paradigm shift? *J Am Coll Cardiol*. 2016;67:2321–9.

10.2.2. Intervention for Mixed AS and MR

1. Gillinov AM, Blackstone EH, Cosgrove DM 3rd, et al. Mitral valve repair with aortic valve replacement is superior to double valve replacement. *J Thorac Cardiovasc Surg*. 2003;125:1372–87.
2. Nombela-Franco L, Ribeiro HB, Urena M, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol*. 2014;63:2643–58.
3. Karamijyan S, Koifman E, Asch FM, et al. Impact of functional versus organic baseline mitral regurgitation on short- and long-term outcomes after transcatheter aortic valve replacement. *Am J Cardiol*. 2016;117:839–46.
4. Chakravarty T, Van Belle E, Jilalawi H, et al. Meta-analysis of the impact of mitral regurgitation on outcomes after transcatheter aortic valve implantation. *Am J Cardiol*. 2015;115:942–9.
5. Cortés C, Amat-Santos IJ, Nombela-Franco L, et al. Mitral regurgitation after transcatheter aortic valve replacement: prognosis, imaging predictors, and potential management. *JACC Cardiovasc Interv*. 2016;9:1603–14.
6. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844–54.
7. Jeong DS, Park PW, Sung K, et al. Long-term clinical impact of functional mitral regurgitation after aortic valve replacement. *Ann Thorac Surg*. 2011;92:1339–45.
8. Ruel M, Kapila V, Price J, et al. Natural history and predictors of outcome in patients with concomitant functional mitral regurgitation at the time of aortic valve replacement. *Circulation*. 2006;114:1541–6.
9. Barbanti M, Webb JG, Hahn RT, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement: insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. *Circulation*. 2013;128:2776–84.
10. Abdelghani M, Abdel-Wahab M, Hemetsberger R, et al. Fate and long-term prognostic implications of mitral regurgitation in patients undergoing transcatheter aortic valve replacement. *Int J Cardiol*. 2019;288:39–43.

10.2.4. Intervention for Mixed MS and AR

1. Gash AK, Carabello BA, Kent RL, et al. Left ventricular performance in patients with coexistent mitral stenosis and aortic insufficiency. *J Am Coll Cardiol*. 1984;3:703–11.
2. Unger P, Pibarot P, Tribouilloy C, et al. Multiple and mixed valvular heart diseases. *Circ Cardiovasc Imaging*. 2018;11:e007862.

3. Gillinov AM, Blackstone EH, Cosgrove DM 3rd, et al. Mitral valve repair with aortic valve replacement is superior to double valve replacement. *J Thorac Cardiovasc Surg*. 2003;125:1372–87.

11. PROSTHETIC VALVES

11.1. Evaluation and Selection of Prosthetic Valves

11.1.1. Diagnosis and Follow-Up of Prosthetic Valves

1. Burstow DJ, Nishimura RA, Bailey KR, et al. Continuous wave Doppler echocardiographic measurement of prosthetic valve gradients. A simultaneous Doppler-catheter correlative study. *Circulation*. 1989;80:504–14.
2. Baumgartner H, Khan S, DeRobertis M, et al. Effect of prosthetic aortic valve design on the Doppler-catheter gradient correlation: an in vitro study of normal St. Jude, Medtronic-Hall, Starr-Edwards and Hancock valves. *J Am Coll Cardiol*. 1992;19:324–32.
3. Vandervoort PM, Greenberg NL, Powell KA, et al. Pressure recovery in bileaflet heart valve prostheses. Localized high velocities and gradients in central and side orifices with implications for Doppler-catheter gradient relation in aortic and mitral position. *Circulation*. 1995;92:3464–72.
4. Dumesnil JG, Honos GN, Lemieux M, et al. Validation and applications of indexed aortic prosthetic valve areas calculated by Doppler echocardiography. *J Am Coll Cardiol*. 1990;16:637–43.
5. Van den Brink RBA. Evaluation of prosthetic heart valves by transesophageal echocardiography: problems, pitfalls, and timing of echocardiography. *Semin Cardiothorac Vasc Anesth*. 2006;10:89–100.
6. Vitarelli A, Conde Y, Cimino E, et al. Assessment of severity of mechanical prosthetic mitral regurgitation by transoesophageal echocardiography. *Heart*. 2004;90:539–44.
7. Kronzon I, Sugeng L, Perk G, et al. Real-time 3-dimensional transesophageal echocardiography in the evaluation of post-operative mitral annuloplasty ring and prosthetic valve dehiscence. *J Am Coll Cardiol*. 2009;53:1543–7.
8. Kim JY, Suh YJ, Han K, et al. Diagnostic value of advanced imaging modalities for the detection and differentiation of prosthetic valve obstruction: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2019;12:2182–92.
9. Salaun E, Mahjoub H, Girerd N, et al. Rate, timing, correlates, and outcomes of hemodynamic valve deterioration after bioprosthetic surgical aortic valve replacement. *Circulation*. 2018;138:971–85.
10. Rahimtoola SH. Choice of prosthetic heart valve in adults an update. *J Am Coll Cardiol*. 2010;55:2413–26.
11. van Geldorp MWA, Eric Jamieson WR, Kappetein AP, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. *J Thorac Cardiovasc Surg*. 2009;137:881–6, 866.e1–5.
12. Salaun E, Mahjoub H, Dahou A, et al. Hemodynamic deterioration of surgically implanted bioprosthetic aortic valves. *J Am Coll Cardiol*. 2018;72:241–51.
13. Dvir D, Bourguignon T, Otto CM, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. *Circulation*. 2018;137:388–99.
14. Douglas PS, Leon MB, Mack MJ, et al. Longitudinal hemodynamics of transcatheter and surgical aortic valves in the PARTNER trial. *JAMA Cardiol*. 2017;2:1197–206.
15. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–84.
16. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–91.
17. Fernandez-Santos S, Thérion A, Pibarot P, et al. Valve hemodynamic performance and myocardial strain after implantation of a third-generation, balloon-expandable, transcatheter aortic valve. *Cardiol J*. 2019 May 20. Online ahead of print. doi:10.5603/CJ.a2019.0049
18. Manoharan G, Van Mieghem NM, Windecker S, et al. 1-Year outcomes with the Evolut R self-expanding transcatheter aortic valve: from the international FORWARD study. *JACC Cardiovasc Interv*. 2018;11:2326–34.

19. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol*. 2018;72:2687–96.
20. Blackman DJ, Saraf S, McCarthy PA, et al. Long-term durability of transcatheter aortic valve prostheses. *J Am Coll Cardiol*. 2019;73:537–45.
21. Søndergaard L, Ihlemann N, Capodanno D, et al. Durability of transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. *J Am Coll Cardiol*. 2019;73:546–53.

11.2.1. Selection of Prosthetic Valve Type: Bioprosthetic Versus Mechanical Valve

1. Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med*. 2017;377:1847–57.
2. Badhwar V, Ofenloch JC, Rovin JD, et al. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg*. 2012;93:748–53.
3. Brown ML, Schaff HV, Lahr BD, et al. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. *J Thorac Cardiovasc Surg*. 2008;135:878–84.
4. van Geldorp MWA, Eric Jamieson WR, Kappetein AP, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. *J Thorac Cardiovasc Surg*. 2009;137:881–6, 866.e1–5.
5. Kulik A, Bédard P, Lam B-K, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. *Eur J Cardiothorac Surg*. 2006;30:485–91.
6. Glaser N, Jackson V, Holzmann MJ, et al. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. *Eur Heart J*. 2016;37:2658–67.
7. Chikwe J, Chiang YP, Egorov NN, et al. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. *JAMA*. 2015;313:1435–42.
8. McClure RS, McGurk S, Cevasco M, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2014;148:1931–9.
9. Chiang YP, Chikwe J, Moskowitz AJ, et al. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA*. 2014;312:1323–9.
10. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. *J Thorac Cardiovasc Surg*. 2014;147:117–26.
11. Bourguignon T, Bouquiaux-Stablo A-L, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 25-year follow-up of 450 implantations. *J Thorac Cardiovasc Surg*. 2014;148:2004–11.e1.
12. Buratto E, Shi WY, Wynne R, et al. Improved survival after the Ross procedure compared with mechanical aortic valve replacement. *J Am Coll Cardiol*. 2018;71:1337–44.
13. El-Hamamsy I, Eryigit Z, Stevens L-M, et al. Long-term outcomes after aortic root replacement versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. *Lancet*. 2010;376:524–31.
14. Martin E, Mohammadi S, Jacques F, et al. Clinical outcomes following the Ross procedure in adults: a 25-year longitudinal study. *J Am Coll Cardiol*. 2017;70:1890–9.
15. Bourguignon T, El Khoury R, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards PERIMOUNT aortic valve in patients aged 60 or younger. *Ann Thorac Surg*. 2015;100:853–9.
16. Tuzcu EM, Kapadia SR, Vemulapalli S, et al. Transcatheter aortic valve replacement of failed surgically implanted bioprostheses: the STS/ACC registry. *J Am Coll Cardiol*. 2018;72:370–82.
17. Ye J, Cheung A, Yamashita M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an 8-year single-center experience. *JACC Cardiovasc Interv*. 2015;8:1735–44.
18. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162–70.
19. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335–44.
20. Coylewright M, Forrest JK, McCabe JM, et al. TAVR in low-risk patients: FDA approval, the new NCD, and shared decision-making. *J Am Coll Cardiol*. 2020;75:1208–11.
21. Hess EP, Coylewright M, Frosch DL, et al. Implementation of shared decision making in cardiovascular care: past, present, and future. *Circ Cardiovasc Qual Outcomes*. 2014;7:797–803.
22. Weber A, Noureddine H, Englberger L, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. *J Thorac Cardiovasc Surg*. 2012;144:1075–83.
23. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152–8.
24. Chan V, Jamieson WRE, Germann E, et al. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2006;131:1267–73.
25. Dunning J, Gao H, Chambers J, et al. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use—an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. *J Thorac Cardiovasc Surg*. 2011;142:776–82.e3.
26. Stassano P, L. DT, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol*. 2009;54:1862–8.
27. Brennan JM, Edwards FH, Zhao Y, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation*. 2013;127:1647–55.
28. Banbury MK, Cosgrove DM 3rd, Thomas JD, et al. Hemodynamic stability during 17 years of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg*. 2002;73:1460–5.
29. Dellgren G, David TE, Raanani E, et al. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc Surg*. 2002;124:146–54.
30. Borger MA, Ivanov J, Armstrong S, et al. Twenty-year results of the Hancock II bioprosthesis. *J Heart Valve Dis*. 2006;15:49–55.
31. Mykén PSU, Bech-Hansen O. A 20-year experience of 1712 patients with the Biocor porcine bioprosthesis. *J Thorac Cardiovasc Surg*. 2009;137:76–81.
32. Mazine A, El-Hamamsy I, Verma S, et al. Ross procedure in adults for cardiologists and cardiac surgeons: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:2761–77.

11.2. Antithrombotic Therapy

1. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89:635–41.
2. Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995;333:11–7.
3. Sun JCJ, Davidson MJ, Lamy A, et al. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet*. 2009;374:565–76.
4. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the Randomized, phase II study to Evaluate the sAFety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (REALIGN). *Am Heart J*. 2012;163:931–7.e1.
5. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–14.
6. Torella M, Torella D, Chiodini P, et al. LOWERing the INTensity of oral anticoagulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the “LOWERING-IT” Trial. *Am Heart J*. 2010;160:171–8.
7. Hering D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. *Chest*. 2005;127:53–9.
8. Acar J, Iung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation*. 1996;94:2107–12.
9. Whitlock RP, Sun JC, Fries SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of

- Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e576S–600S.
10. Horstkotte D, Scharf RE, Schultheiss HP. Intracardiac thrombosis: patient-related and device-related factors. *J Heart Valve Dis.* 1995;4:114–20.
 11. Pruefer D, Dahm M, Dohmen G, et al. Intensity of oral anticoagulation after implantation of St. Jude Medical mitral or multiple valve replacement: lessons learned from GELIA (GELIA 5). *Eur Heart J Suppl.* 2001;3:Q39–43.
 12. Rodés-Cabau J, Masson J-B, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. *JACC Cardiovasc Interv.* 2017;10:1357–65.
 13. Zuo W, Yang M, He Y, et al. Single or dual antiplatelet therapy after transcatheter aortic valve replacement: an updated systemic review and meta-analysis. *J Thorac Dis.* 2019;11:959–68.
 14. Maes F, Stabile E, Ussia GP, et al. Meta-analysis comparing single versus dual antiplatelet therapy following transcatheter aortic valve implantation. *Am J Cardiol.* 2018;122:310–5.
 15. Heras M, Chesebro JH, Fuster V, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. *J Am Coll Cardiol.* 1995;25:1111–9.
 16. Colli A, Mestres CA, Castella M, et al. Comparing warfarin to aspirin (WoA) after aortic valve replacement with the St. Jude Medical Epic heart valve bioprosthesis: results of the WoA Epic pilot trial. *J Heart Valve Dis.* 2007;16:667–71.
 17. Aramendi JJ, Mestres C-A, Martínez-León J, et al. Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (TRAC): prospective, randomized, co-operative trial. *Eur J Cardiothorac Surg.* 2005;27:854–60.
 18. Nuñez L, Gil Aguado M, Larrea JL, et al. Prevention of thromboembolism using aspirin after mitral valve replacement with porcine bioprosthesis. *Ann Thorac Surg.* 1984;37:84–7.
 19. Tiede DJ, Nishimura RA, Gastineau DA, et al. Modern management of prosthetic valve anticoagulation. *Mayo Clin Proc.* 1998;73:665–80.
 20. Mérie C, Køber L, Skov Olsen P, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA.* 2012;308:2118–25.
 21. Russo A, Grigioni F, Averbosch J-F, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J Am Coll Cardiol.* 2008;51:1203–11.
 22. Egbe AC, Pislaru SV, Pelliikka PA, et al. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol.* 2015;66:2285–94.
 23. Chakravarty T, Patel A, Kapadia S, et al. Anticoagulation after surgical or transcatheter bioprosthetic aortic valve replacement. *J Am Coll Cardiol.* 2019;74:1190–200.
 24. Sundt TM, Zehr KJ, Dearani JA, et al. Is early anticoagulation with warfarin necessary after bioprosthetic aortic valve replacement? *J Thorac Cardiovasc Surg.* 2005;129:1024–31.
 25. El Bardissi AW, DiBardino DJ, Chen FY, et al. Is early antithrombotic therapy necessary in patients with bioprosthetic aortic valves in normal sinus rhythm? *J Thorac Cardiovasc Surg.* 2010;139:1137–45.
 26. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev.* 2013;CD003464.
 27. Puskas J, Gerdtsch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg.* 2014;147:1202–10.
 28. Puskas JD, Gerdtsch M, Nichols D, et al. Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. *J Am Coll Cardiol.* 2018;71:2717–26.
 29. Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol.* 2011;108:1772–6.
 30. Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med.* 2020;382:120–9.
 31. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med.* 2015;373:2015–24.
 32. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv.* 2017;10:686–97.
 33. Jochheim D, Barbanti M, Capretti G, et al. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2019;12:1566–76.
 34. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–51.
 35. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–104.
 36. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med.* 2011;365:883–91.
 37. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–92.
 38. Edmunds LH Jr. Thrombotic and bleeding complications of prosthetic heart valves. *Ann Thorac Surg.* 1987;44:430–45.
 39. Capodanno D, Angiolillo DJ. Antiplatelet therapy after implantation of bioresorbable vascular scaffolds: a review of the published data, practical recommendations, and future directions. *JACC Cardiovasc Interv.* 2017;10:425–37.
 40. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med.* 2015;373:823–33.

11.3. Bridging Therapy

1. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e326S–50S.
2. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med.* 1997;336:1506–11.
3. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. Observations in 180 operations. *JAMA.* 1978;239:738–9.
4. Lankiewicz MW, Hays J, Friedman KD, et al. Urgent reversal of warfarin with prothrombin complex concentrate. *J Thromb Haemost.* 2006;4:967–70.
5. Renda G, Ricci F, Giugliano RP, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol.* 2017;69:1363–71.
6. Hammerstingl C, Tripp C, Schmidt H, et al. Periprocedural bridging therapy with low-molecular-weight heparin in chronically anticoagulated patients with prosthetic mechanical heart valves: experience in 116 patients from the prospective BRAVE registry. *J Heart Valve Dis.* 2007;16:285–92.
7. Spyropoulos AC, Turpie AG, Dunn AS, et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). *Am J Cardiol.* 2008;102:883–9.
8. Pengo V, Cucchini U, Denas G, et al. Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. *Circulation.* 2009;119:2920–7.
9. Daniels PR, McBane RD, Litin SC, et al. Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. *Thromb Res.* 2009;124:300–5.
10. Bui HT, Krishnaswami A, Le CU, et al. Comparison of safety of subcutaneous enoxaparin as outpatient anticoagulation bridging therapy in patients with a mechanical heart valve versus patients with nonvalvular atrial fibrillation. *Am J Cardiol.* 2009;104:1429–33.
11. Bitekier M, Tekkesin AI, Can MM, et al. Outcome of noncardiac and non-vascular surgery in patients with mechanical heart valves. *Am J Cardiol.* 2012;110:562–7.
12. Weiss A, Brose S, Ploetze K, et al. Half-dose enoxaparin vs. full-dose enoxaparin for postoperative bridging therapy in patients after cardiac surgery: which dose regimen should be preferred? *Clin Hemorheol Microcirc.* 2013;54:249–58.
13. Pengo V, Palareti G, Cucchini U, et al. Low-intensity oral anticoagulant plus low-dose aspirin during the first six months versus standard-intensity oral anticoagulant therapy after mechanical heart valve replacement: a pilot study of low-intensity warfarin and aspirin in cardiac prostheses (LI-WACAP). *Clin Appl Thromb Hemost.* 2007;13:241–8.
14. Hjeltnestrom L, Labaf A. Prophylactic doses of low-molecular weight heparin as periprocedural bridging therapy in mechanical heart valve patients. *Thromb Res.* 2018;163:180–4.
15. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med.* 2015;373:823–33.

11.4. Excessive Anticoagulation and Serious Bleeding With Prosthetic Valves

- Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–20.
- Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373:2413–24.
- Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131–41.
- Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380:1326–35.
- Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–41.
- Genewein U, Haerberli A, Straub PW, et al. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. *Br J Haematol*. 1996;92:479–85.
- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70:3042–67.
- Tazarourte K, Riou B, Tremey B, et al. Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). *Crit Care*. 2014;18:R81.
- Tsu LV, Dienes JE, Dager WE. Vitamin K dosing to reverse warfarin based on INR, route of administration, and home warfarin dose in the acute/critical care setting. *Ann Pharmacother*. 2012;46:1617–26.
- Pernod G, Godiér A, Gozalo C, et al. French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding). *Thromb Res*. 2010;126:e167–74.
- Weibert RT, Le DT, Kayser SR, et al. Correction of excessive anticoagulation with low-dose oral vitamin K1. *Ann Intern Med*. 1997;126:959–62.
- Yiu K-H, Siu C-W, Jim M-H, et al. Comparison of the efficacy and safety profiles of intravenous vitamin K and fresh frozen plasma as treatment of warfarin-related over-anticoagulation in patients with mechanical heart valves. *Am J Cardiol*. 2006;97:409–11.
- Khatib R, Ludwikowska M, Witt DM, et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. *Blood Adv*. 2019;3:789–96.

11.5. Thromboembolic Events With Prosthetic Valves

- Dangas GD, Weitz JI, Giustino G, et al. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68:2670–89.
- Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–92.
- Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–24.
- Søndergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J*. 2017;38:2201–7.

11.6. Acute Mechanical Valve Thrombosis

11.6.1. Diagnosis of Acute Mechanical Valve Thrombosis

- Montorsi P, De Bernardi F, Muratori M, et al. Role of cine-fluoroscopy, transthoracic, and transesophageal echocardiography in patients with suspected prosthetic heart valve thrombosis. *Am J Cardiol*. 2000;85:58–64.
- Muratori M, Montorsi P, Teruzzi G, et al. Feasibility and diagnostic accuracy of quantitative assessment of mechanical prostheses leaflet motion by transthoracic and transesophageal echocardiography in suspected prosthetic valve dysfunction. *Am J Cardiol*. 2006;97:94–100.
- Cianciulli TE, Lax JA, Beck MA, et al. Cinefluoroscopic assessment of mechanical disc prostheses: its value as a complementary method to echocardiography. *J Heart Valve Dis*. 2005;14:664–73.

- Symersky P, Budde RPJ, de Mol BAJM, et al. Comparison of multidetector-row computed tomography to echocardiography and fluoroscopy for evaluation of patients with mechanical prosthetic valve obstruction. *Am J Cardiol*. 2009;104:1128–34.
- Bapat V, Attia R, Redwood S, et al. Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprostheses: technical considerations and results. *J Thorac Cardiovasc Surg*. 2012;144:1372–9.
- Gündüz S, Özkan M, Kalçık M, et al. Sixty-four-section cardiac computed tomography in mechanical prosthetic heart valve dysfunction: thrombus or pannus. *Circ Cardiovasc Imaging*. 2015;8:e003246.
- Suh YJ, Lee S, Im DJ, et al. Added value of cardiac computed tomography for evaluation of mechanical aortic valve: emphasis on evaluation of pannus with surgical findings as standard reference. *Int J Cardiol*. 2016;214:454–60.
- Dangas GD, Weitz JI, Giustino G, et al. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68:2670–89.
- Barbetteas J, Nagueh SF, Pitsavos C, et al. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol*. 1998;32:1410–7.
- Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. Developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014.
- Özkan M, Gündüz S, Biterker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *JACC Cardiovasc Imaging*. 2013;6:206–16.
- Suchá D, Symersky P, Tanis W, et al. Multimodality imaging assessment of prosthetic heart valves. *Circ Cardiovasc Imaging*. 2015;8:e003703.

11.6.2. Intervention

- Cáceres-Lóriga FM, Pérez-López H, Morlans-Hernández K, et al. Thrombolysis as first choice therapy in prosthetic heart valve thrombosis. A study of 68 patients. *J Thromb Thrombolysis*. 2006;21:185–90.
- Karthikeyan G, Senguttuvan NB, Joseph J, et al. Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies. *Eur Heart J*. 2013;34:1557–66.
- Keuleers S, Herijgers P, Herregods M-C, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. *Am J Cardiol*. 2011;107:275–9.
- Nagy A, Dénes M, Lengyel M. Predictors of the outcome of thrombolytic therapy in prosthetic mitral valve thrombosis: a study of 62 events. *J Heart Valve Dis*. 2009;18:268–75.
- Özkan M, Çakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation*. 2013;128:532–40.
- Özkan M, Gündüz S, Biterker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *JACC Cardiovasc Imaging*. 2013;6:206–16.
- Roudaut R, Lafitte S, Roudaut M-F, et al. Management of prosthetic heart valve obstruction: fibrinolysis versus surgery. Early results and long-term follow-up in a single-centre study of 263 cases. *Arch Cardiovasc Dis*. 2009;102:269–77.
- Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *J Am Coll Cardiol*. 2004;43:77–84.
- Bade AS, Shaikh SSA, Khemani H, et al. Thrombolysis is an effective and safe therapy in stuck mitral valves with delayed presentation as well as hemodynamically unstable patients: a single centre study. *Cardiol Res*. 2018;9:161–4.
- Pragt H, van Melle JP, Javadikasgari H, et al. Mechanical valves in the pulmonary position: an international retrospective analysis. *J Thorac Cardiovasc Surg*. 2017;154:1371–8.e1.

11. Taherkhani M, Hashemi SR, Hekmat M, et al. Thrombolytic therapy for right-sided mechanical pulmonic and tricuspid valves: the largest survival analysis to date. *Tex Heart Inst J*. 2015;42:543–7.
12. Kumar BM, Gnanaraj JP, Swaminathan N, et al. Assessment of hemodynamic and clinical response in thrombolytic therapy for prosthetic valve thrombosis. *Indian Heart J*. 2017;69:S6.
13. Özkan M, Gündüz S, Gürsoy OM, et al. Ultraslow thrombolytic therapy: a novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcomE: the Ultra-slow PROMETEE trial. *Am Heart J*. 2015;170:409–18.
14. Roudaut R, Lafitte S, Roudaut M-F, et al. Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol*. 2003;41:653–8.

11.7. Bioprosthetic Valve Thrombosis

11.7.1. Diagnosis of Bioprosthetic Valve Thrombosis

1. Puri R, Auffret V, Rodés-Cabau J. Bioprosthetic valve thrombosis. *J Am Coll Cardiol*. 2017;69:2193–211.
2. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation*. 2001;103:1535–41.
3. Dangas GD, Weitz JI, Giustino G, et al. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68:2670–89.
4. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–97.
5. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–92.
6. Pislaru SV, Hussain I, Pellikka PA, et al. Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. *Eur J Cardiothorac Surg*. 2015;47:725–32.

11.7.2. Medical Therapy

1. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–24.
2. Jander N, Kienle R-P, Kayser G, et al. Usefulness of phenprocoumon for the treatment of obstructing thrombus in bioprostheses in the aortic valve position. *Am J Cardiol*. 2012;109:257–62.
3. Butnaru A, Shaheen J, Tzivoni D, et al. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. *Am J Cardiol*. 2013;112:1439–44.
4. Pislaru SV, Hussain I, Pellikka PA, et al. Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. *Eur J Cardiothorac Surg*. 2015;47:725–32.
5. De Marchena E, Mesa J, Pomenti S, et al. Thrombus formation following transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2015;8:728–39.
6. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–97.
7. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8:e001779.
8. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–92.

11.8. Prosthetic Valve Stenosis

11.8.1. Diagnosis of Prosthetic Valve Stenosis

1. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. Developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart

- Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014.
2. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:589–90.
3. Puri R, Auffret V, Rodés-Cabau J. Bioprosthetic valve thrombosis. *J Am Coll Cardiol*. 2017;69:2193–211.
4. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation*. 2001;103:1535–41.
5. Dangas GD, Weitz JI, Giustino G, et al. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68:2670–89.
6. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–97.
7. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–92.
8. Barbetseas J, Nagueh SF, Pitsavos C, et al. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol*. 1998;32:1410–7.
9. Dvir D, Bourguignon T, Otto CM, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. *Circulation*. 2018;137:388–99.
10. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation*. 2009;119:1034–48.
11. Koene BM, Soliman Hamad MA, Bouma W, et al. Impact of prosthesis-patient mismatch on early and late mortality after aortic valve replacement. *J Cardiothorac Surg*. 2013;8:96.

11.8.2. Intervention for Prosthetic Valve Stenosis

1. Leontyev S, Borger MA, Davierwala P, et al. Redo aortic valve surgery: early and late outcomes. *Ann Thorac Surg*. 2011;91:1120–6.
2. Kaneko T, Vassileva CM, Englum B, et al. Contemporary outcomes of repeat aortic valve replacement: a benchmark for transcatheter valve-in-valve procedures. *Ann Thorac Surg*. 2015;100:1298–304.
3. Jausaud N, Gariboldi V, Grisoli D, et al. Risk of reoperation for mitral bioprosthesis dysfunction. *J Heart Valve Dis*. 2012;21:56–60.
4. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162–70.
5. Ye J, Cheung A, Yamashita M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an 8-year single-center experience. *JACC Cardiovasc Interv*. 2015;8:1735–44.
6. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–24.
7. Jander N, Kienle R-P, Kayser G, et al. Usefulness of phenprocoumon for the treatment of obstructing thrombus in bioprostheses in the aortic valve position. *Am J Cardiol*. 2012;109:257–62.
8. Butnaru A, Shaheen J, Tzivoni D, et al. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. *Am J Cardiol*. 2013;112:1439–44.
9. Pislaru SV, Hussain I, Pellikka PA, et al. Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. *Eur J Cardiothorac Surg*. 2015;47:725–32.
10. De Marchena E, Mesa J, Pomenti S, et al. Thrombus formation following transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2015;8:728–39.
11. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv*. 2017;10:686–97.
12. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8:e001779.
13. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–92.
14. Gozdek M, Raffa GM, Suwalski P, et al. Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve

bioprostheses: systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2018;53:495–504.

15. Takagi H, Hari Y, Kawai N, et al. Meta-analysis of transcatheter aortic valve implantation for bicuspid versus tricuspid aortic valves. *J Cardiol*. 2019;74:40–8.
16. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. *J Thorac Cardiovasc Surg*. 2014;147:117–26.
17. Petrescu I, Egbe AC, Ionescu F, et al. Long-term outcomes of anticoagulation for bioprosthetic valve thrombosis. *J Am Coll Cardiol*. 2020;75:857–66.

11.9. Prosthetic Valve Regurgitation

1. Dvir D, Bourguignon T, Otto CM, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. *Circulation*. 2018;137:388–99.
2. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. Developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014.

11.9.1. Diagnosis of Prosthetic Valve Regurgitation

1. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. Developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014.
2. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:589–90.
3. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2019;32:431–75.
4. Hascoet S, Smolka G, Bagate F, et al. Multimodality imaging guidance for percutaneous paravalvular leak closure: Insights from the multi-centre FFPP register. *Arch Cardiovasc Dis*. 2018;111:421–31.
5. García-Fernández MA, Cortés M, García-Robles JA, et al. Utility of real-time three-dimensional transesophageal echocardiography in evaluating the success of percutaneous transcatheter closure of mitral paravalvular leaks. *J Am Soc Echocardiogr*. 2010;23:26–32.
6. Nombela-Franco L, Ribeiro HB, Urena M, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol*. 2014;63:2643–58.
7. Ruiz CE, Hahn RT, Berrebi A, et al. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis: an expert statement. *J Am Coll Cardiol*. 2017;69:2067–87.
8. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2012;25:3–46.
9. Ruparel N, Cao J, Newton JD, et al. Paravalvular leak closure under intracardiac echocardiographic guidance. *Catheter Cardiovasc Interv*. 2018;91:958–65.

11.9.3. Intervention

1. Akins CW, Bitondo JM, Hilgenberg AD, et al. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. *J Heart Valve Dis*. 2005;14:792–9.

2. Kaneko T, Vassileva CM, Englum B, et al. Contemporary outcomes of repeat aortic valve replacement: a benchmark for transcatheter valve-in-valve procedures. *Ann Thorac Surg*. 2015;100:1298–304.
3. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. *J Thorac Cardiovasc Surg*. 2014;147:117–26.
4. Jaussaud N, Gariboldi V, Grisoli D, et al. Risk of reoperation for mitral bioprosthesis dysfunction. *J Heart Valve Dis*. 2012;21:56–60.
5. Sorajja P, Cabalka AK, Hagler DJ, et al. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. *Circ Cardiovasc Interv*. 2011;4:314–21.
6. Sorajja P, Cabalka AK, Hagler DJ, et al. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. *J Am Coll Cardiol*. 2011;58:2218–24.
7. Alkhouli M, Rihal CS, Zack CJ, et al. Transcatheter and surgical management of mitral paravalvular leak: long-term outcomes. *JACC Cardiovasc Interv*. 2017;10:1946–56.
8. Alkhouli M, Zack CJ, Sarraf M, et al. Successful percutaneous mitral paravalvular leak closure is associated with improved midterm survival. *Circ Cardiovasc Interv*. 2017;10:e005730.
9. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. *J Am Coll Cardiol*. 2011;58:2210–7.
10. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162–70.
11. Phan K, Zhao D-F, Wang N, et al. Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. *J Thorac Dis*. 2016;8:E83–93.
12. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation*. 2010;121:1848–57.
13. Kaneko T, Vassileva CM, Englum B, et al. Contemporary outcomes of repeat aortic valve replacement: a benchmark for transcatheter valve-in-valve procedures. *Ann Thorac Surg*. 2015;100:1298–304.
14. Shah S, Alashi A, Pettersson GB, et al. Characteristics and longer-term outcomes of paravalvular leak after aortic and mitral valve surgery. *J Thorac Cardiovasc Surg*. 2019;157:1785–92.e1.
15. Bouhout I, Mazine A, Ghoneim A, et al. Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position. *J Thorac Cardiovasc Surg*. 2016;151:1260–6.e1.
16. STS online risk calculator. Available at: <http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx> 2013. Accessed June 20, 2020.
17. Takagi H, Hari Y, Kawai N, et al. Meta-analysis of transcatheter aortic valve implantation for bicuspid versus tricuspid aortic valves. *J Cardiol*. 2019;74:40–8.
18. Gozdek M, Raffa GM, Suwalski P, et al. Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve bioprostheses: systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2018;53:495–504.

12. INFECTIVE ENDOCARDITIS

12.2. Diagnosis of IE

1. Steckelberg JM, Wilson WR. Risk factors for infective endocarditis. *Infect Dis Clin North Am*. 1993;7:9–19.
2. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Duke Endocarditis Service*. *Am J Med*. 1994;96:200–9.
3. Kupferwasser LI, Darius H, Müller AM, et al. Diagnosis of culture-negative endocarditis: the role of the Duke criteria and the impact of transesophageal echocardiography. *Am Heart J*. 2001;142:146–52.
4. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–8.
5. Pérez-Vázquez A, Fariñas MC, García-Palomo JD, et al. Evaluation of the Duke criteria in 93 episodes of prosthetic valve endocarditis: could sensitivity be improved? *Arch Intern Med*. 2000;160:1185–91.
6. Lukes AS, Bright DK, Durack DT. Diagnosis of infective endocarditis. *Infect Dis Clin North Am*. 1993;7:1–8.
7. Dodds GA, Sexton DJ, Durack DT, et al. Negative predictive value of the Duke criteria for infective endocarditis. *Am J Cardiol*. 1996;77:403–7.
8. Bayer AS. Diagnostic criteria for identifying cases of endocarditis—revisiting the Duke criteria two years later. *Clin Infect Dis*. 1996;23:303–4.

9. Prendergast BD. Diagnostic criteria and problems in infective endocarditis. *Heart*. 2004;90:611–3.
10. Tsutsumi T, Eron LJ. Clinical use of the Duke criteria in patients with suspected infective endocarditis and negative transesophageal echocardiograms. *Infect Dis Clin Pract*. 2012;20:315–8.
11. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–73.
12. Haldar SM, O'Gara PT. Infective endocarditis: diagnosis and management. *Nat Clin Pract Cardiovasc Med*. 2006;3:310–7.
13. Bashore TM, Cabell C, Fowler V Jr. Update on infective endocarditis. *Curr Probl Cardiol*. 2006;31:274–352.
14. Mügge A, Daniel WG, Frank G, et al. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol*. 1989;14:631–8.
15. Burger AJ, Peart B, Jabi H, et al. The role of two-dimensional echocardiography in the diagnosis of infective endocarditis [corrected]. *Angiology*. 1991;42:552–60.
16. Irani WN, Grayburn PA, Afridi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. *Am J Cardiol*. 1996;78:101–3.
17. Liu Y-W, Tsai W-C, Hsu C-H, et al. Judicious use of transthoracic echocardiography in infective endocarditis screening. *Can J Cardiol*. 2009;25:703–5.
18. Kemp WE Jr, Citrin B, Byrd BF 3rd. Echocardiography in infective endocarditis. *South Med J*. 1999;92:744–54.
19. Rubenson DS, Tucker CR, Stinson EB, et al. The use of echocardiography in diagnosing culture-negative endocarditis. *Circulation*. 1981;64:641–6.
20. Shapiro SM, Young E, De Guzman S, et al. Transesophageal echocardiography in diagnosis of infective endocarditis. *Chest*. 1994;105:377–82.
21. Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach. A prospective study. *Eur Heart J*. 1988;9:43–53.
22. Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with *Staphylococcus aureus* bacteraemia: the value of screening with echocardiography. *Eur J Echocardiogr*. 2011;12:414–20.
23. Reynolds HR, Jagen MA, Tunick PA, et al. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. *J Am Soc Echocardiogr*. 2003;16:67–70.
24. Daniel WG, Mügge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med*. 1991;324:795–800.
25. Sochowski RA, Chan KL. Implication of negative results on a monoplane transesophageal echocardiographic study in patients with suspected infective endocarditis. *J Am Coll Cardiol*. 1993;21:216–21.
26. Shively BK, Gurule FT, Roldan CA, et al. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. *J Am Coll Cardiol*. 1991;18:391–7.
27. Pedersen WR, Walker M, Olson JD, et al. Value of transesophageal echocardiography as an adjunct to transthoracic echocardiography in evaluation of native and prosthetic valve endocarditis. *Chest*. 1991;100:351–6.
28. Ronderos RE, Portis M, Stoermann W, et al. Are all echocardiographic findings equally predictive for diagnosis in prosthetic endocarditis? *J Am Soc Echocardiogr*. 2004;17:664–9.
29. Roe MT, Abramson MA, Li J, et al. Clinical information determines the impact of transesophageal echocardiography on the diagnosis of infective endocarditis by the duke criteria. *Am Heart J*. 2000;139:945–51.
30. Karalis DG, Bansal RC, Hauck AJ, et al. Transesophageal echocardiographic recognition of subaortic complications in aortic valve endocarditis. Clinical and surgical implications. *Circulation*. 1992;86:353–62.
31. El-Ahdab F, Benjamin DK Jr, Wang A, et al. Risk of endocarditis among patients with prosthetic valves and *Staphylococcus aureus* bacteremia. *Am J Med*. 2005;118:225–9.
32. Douglas PS, Garcia MJ, Haines DE, et al. ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2011;57:1126–66.
33. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation*. 2003;108:1146–62.
34. Vilacosta I, Graupner C, San Román JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. *J Am Coll Cardiol*. 2002;39:1489–95.
35. Hoen B, Alla F, Seltou-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA*. 2002;288:75–81.
36. Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Ann Intern Med*. 1999;130:810–20.
37. Fagman E, Perrotta S, Bech-Hanssen O, et al. ECG-gated computed tomography: a new role for patients with suspected aortic prosthetic valve endocarditis. *Eur Radiol*. 2012;22:2407–14.
38. Rohmann S, Erbel R, Darius H, et al. Prediction of rapid versus prolonged healing of infective endocarditis by monitoring vegetation size. *J Am Soc Echocardiogr*. 1991;4:465–74.
39. Massoué P-L, Reuter S, Lafitte S, et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. *Pacing Clin Electrophysiol*. 2007;30:12–9.
40. Narducci ML, Pelargonio G, Russo E, et al. Usefulness of intracardiac echocardiography for the diagnosis of cardiovascular implantable electronic device-related endocarditis. *J Am Coll Cardiol*. 2013;61:1398–405.
41. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162:90–4.
42. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2009;30:2369–413.
43. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318–30.
44. Lengyel M. The impact of transesophageal echocardiography on the management of prosthetic valve endocarditis: experience of 31 cases and review of the literature. *J Heart Valve Dis*. 1997;6:204–11.
45. Bayer AS. Infective endocarditis. *Clin Infect Dis*. 1993;17:313–20.
46. Ghatak A, Pullatt R, Vyse S, et al. Appropriateness criteria are an imprecise measure for repeat echocardiograms. *Echocardiography*. 2011;28:131–5.
47. Shapira Y, Weisenberg DE, Vaturi M, et al. The impact of intraoperative transesophageal echocardiography in infective endocarditis. *Isr Med Assoc J*. 2007;9:299–302.
48. Yao F, Han L, Xu Z, et al. Surgical treatment of multivalvular endocarditis: twenty-one-year single center experience. *J Thorac Cardiovasc Surg*. 2009;137:1475–80.
49. Eltzhig HK, Rosenberger P, Löffler M, et al. Impact of intraoperative transesophageal echocardiography on surgical decisions in 12,566 patients undergoing cardiac surgery. *Ann Thorac Surg*. 2008;85:845–52.
50. Silva F, Arruda R, Nobre A, et al. Impact of intraoperative transesophageal echocardiography in cardiac surgery: retrospective analysis of a series of 850 examinations. *Rev Port Cardiol*. 2010;29:1363–82.
51. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380:415–24.
52. Watanakunakorn C. *Staphylococcus aureus* endocarditis at a community teaching hospital, 1980 to 1991. An analysis of 106 cases. *Arch Intern Med*. 1994;154:2330–5.
53. Abraham J, Mansour C, Veledar E, et al. *Staphylococcus aureus* bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin-sensitive *S aureus* and methicillin-resistant *S aureus* bacteremia. *Am Heart J*. 2004;147:536–9.
54. Kaasch AJ, Fowler VG Jr, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2011;53:1–9.
55. Petti CA, Fowler VG Jr. *Staphylococcus aureus* bacteremia and endocarditis. *Cardiol Clin*. 2003;21:219–33, vii.
56. Fowler VG Jr, Sanders LL, Kong LK, et al. Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. *Clin Infect Dis*. 1999;28:106–14.
57. San Martín J, Sarriá C, de las Cuevas C, et al. Relevance of clinical presentation and period of diagnosis in prosthetic valve endocarditis. *J Heart Valve Dis*. 2010;19:131–8.

58. Knudsen JB, Fuursted K, Petersen E, et al. Failure of clinical features of low probability endocarditis. The early echo remains essential. *Scand Cardiovasc J*. 2011;45:133–8.
59. Lamas CC, Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. *Clin Infect Dis*. 1997;25:713–9.
60. Piper C, Körfer R, Horstkotte D. Prosthetic valve endocarditis. *Heart*. 2001;85:590–3.
61. Feuchtner GM, Stolzmann P, Dichtl W, et al. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. *J Am Coll Cardiol*. 2009;53:436–44.
62. Gahide G, Bommart S, Demaria R, et al. Preoperative evaluation in aortic endocarditis: findings on cardiac CT. *AJR Am J Roentgenol*. 2010;194:574–8.
63. Lentini S, Monaco F, Tancredi F, et al. Aortic valve infective endocarditis: could multi-detector CT scan be proposed for routine screening of concomitant coronary artery disease before surgery? *Ann Thorac Surg*. 2009;87:1585–7.
64. Schoepf U, White R, Woodard P, et al. ACR Appropriateness Criteria®: Suspected Infective Endocarditis. Agency for Healthcare Research and Quality, 2011.
65. Kung VWS, Jarral OA, Shipolini AR, et al. Is it safe to perform coronary angiography during acute endocarditis? *Interact Cardiovasc Thorac Surg*. 2011;13:158–67.
66. Cianciulli TE, Lax JA, Beck MA, et al. Cinefluoroscopic assessment of mechanical disc prostheses: its value as a complementary method to echocardiography. *J Heart Valve Dis*. 2005;14:664–73.
67. Aoyagi S, Nishimi M, Kawano H, et al. Obstruction of St Jude Medical valves in the aortic position: significance of a combination of cineradiography and echocardiography. *J Thorac Cardiovasc Surg*. 2000;120:142–7.
68. Vogel W, Stoll HP, Bay W, et al. Cineradiography for determination of normal and abnormal function in mechanical heart valves. *Am J Cardiol*. 1993;71:225–32.
69. Mahmood M, Kendi AT, Ajmal S, et al. Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis. *J Nucl Cardiol*. 2019;26:922–35.
70. de Camargo RA, Sommer Bitencourt M, Meneghetti JC, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis of left-sided endocarditis: native vs prosthetic valves endocarditis. *Clin Infect Dis*. 2020;70:583–94.
71. Scholtens AM, Swart LE, Verberne HJ, et al. Dual-time-point FDG PET/CT imaging in prosthetic heart valve endocarditis. *J Nucl Cardiol*. 2018;25:1960–7.
72. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol*. 1997;30:1072–8.
73. Sullenberger AL, Avedissian LS, Kent SM. Importance of transesophageal echocardiography in the evaluation of *Staphylococcus aureus* bacteremia. *J Heart Valve Dis*. 2005;14:23–8.
74. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–55.
75. Capp R, Chang Y, Brown DFM. Effective antibiotic treatment prescribed by emergency physicians in patients admitted to the intensive care unit with severe sepsis or septic shock: where is the gap? *J Emerg Med*. 2011;41:573–80.
76. Garza D, Becan-McBride K. *Phlebotomy Handbook*. Stamford, CT: Appleton & Lange; 1998.
77. Baron EJ, Scott JD, Tompkins LS. Prolonged incubation and extensive subculturing do not increase recovery of clinically significant microorganisms from standard automated blood cultures. *Clin Infect Dis*. 2005;41:1677–80.
78. Houpiakian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. *Medicine (Baltimore)*. 2005;84:162–73.
2. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. *Circulation*. 2005;111:e394–e434.
3. López J, Sevilla T, Vilacosta I, et al. Prognostic role of persistent positive blood cultures after initiation of antibiotic therapy in left-sided infective endocarditis. *Eur Heart J*. 2013;34:1749–54.
4. Partridge DG, O'Brien E, Chapman ALN. Outpatient parenteral antibiotic therapy for infective endocarditis: a review of 4 years' experience at a UK centre. *Postgrad Med J*. 2012;88:377–81.
5. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc*. 2011;86:156–67.
6. DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by *Staphylococcus aureus* in injection drug users. *Ann Intern Med*. 1994;121:873–6.
7. Martí-Carvajal AJ, Dayer M, Conterno LO, et al. A comparison of different antibiotic regimens for the treatment of infective endocarditis. *Cochrane Database Syst Rev*. 2016;4:CD009880.
8. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med*. 2014;174:1369–76.
9. Englander H, Weimer M, Solotaroff R, et al. Planning and designing the Improving Addiction Care Team (IMPACT) for hospitalized adults with substance use disorder. *J Hosp Med*. 2017;12:339–42.
10. Schranz AJ, Fleischauer A, Chu VH, et al. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170:31–40.
11. Whitlock RP, Sun JC, Fremes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e576S–600S.
12. Masuda J, Yutani C, Waki R, et al. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. *Stroke*. 1992;23:843–50.
13. Tornos P, Almirante B, Mirabet S, et al. Infective endocarditis due to *Staphylococcus aureus*: deleterious effect of anticoagulant therapy. *Arch Intern Med*. 1999;159:473–5.
14. Carpenter JL, McAllister CK. Anticoagulation in prosthetic valve endocarditis. *South Med J*. 1983;76:1372–5.
15. Lieberman A, Hass WK, Pinto R, et al. Intracranial hemorrhage and infarction in anticoagulated patients with prosthetic heart valves. *Stroke*. 1978;9:18–24.
16. Wilson WR, Geraci JE, Danielson GK, et al. Anticoagulant therapy and central nervous system complications in patients with prosthetic valve endocarditis. *Circulation*. 1978;57:1004–7.
17. Ananthasubramanian K, Beattie JN, Rosman HS, et al. How safely and for how long can warfarin therapy be withheld in prosthetic heart valve patients hospitalized with a major hemorrhage? *Chest*. 2001;119:478–84.
18. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. *Clin Infect Dis*. 2008;47:23–30.
19. Tunkel AR, Kaye D. Neurologic complications of infective endocarditis. *Neurol Clin*. 1993;11:419–40.
20. Immediate anticoagulation of embolic stroke: brain hemorrhage and management options. Cerebral Embolism Study Group. *Stroke*. 1984;15:779–89.
21. Kamalakannan D, Beeai M, Gardin JM, et al. Anticoagulation in infective endocarditis: a survey of infectious disease specialists and cardiologists. *Infect Dis Clin Pract*. 2005;13:122–6.
22. Nagpal A, Sohail MR, Steckelberg JM. Prosthetic valve endocarditis: state of the heart. *Clin Invest*. 2012;2:803–17.
23. Thuny F, Avierinos J-F, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. *Eur Heart J*. 2007;28:1155–61.
24. Duval X, Lung B, Klein I, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. *Ann Intern Med*. 2010;152:497–504, W175.
25. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380:415–24.
26. Pruitt AA, Rubin RH, Karchmer AW, et al. Neurologic complications of bacterial endocarditis. *Medicine (Baltimore)*. 1978;57:329–43.

12.3. Medical Therapy

1. Gould FK, Denning DW, Elliott TSJ, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2012;67:269–89.

27. Chan K-L, Tam J, Dumesnil JG, et al. Effect of long-term aspirin use on embolic events in infective endocarditis. *Clin Infect Dis*. 2008;46:37–41.
28. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med*. 2007;120:700–5.
29. Rasmussen RV, Snygg-Martin U, Olaison L, et al. Major cerebral events in *Staphylococcus aureus* infective endocarditis: is anticoagulant therapy safe? *Cardiology*. 2009;114:284–91.
30. Sonnevile R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDO-cardite en REAnimation prospective multicenter study. *Crit Care Med*. 2011;39:1474–81.
31. Chan K-L, Dumesnil JG, Cujec B, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol*. 2003;42:775–80.
32. Anavekar NS, Tleyjeh IM, Anavekar NS, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. *Clin Infect Dis*. 2007;44:1180–6.
33. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke*. 2005;36:1588–93.
34. He J, Whelton PK, Vu B, et al. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA*. 1998;280:1930–5.
35. Werner M, Andersson R, Olaison L, et al. A clinical study of culture-negative endocarditis. *Medicine (Baltimore)*. 2003;82:263–73.
36. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296–327.
37. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2009;30:2369–413.
38. Park CB, Greason KL, Suri RM, et al. Fate of nonreplaced sinuses of Valsalva in bicuspid aortic valve disease. *J Thorac Cardiovasc Surg*. 2011;142:278–84.
39. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162:90–4.
40. Tleyjeh IM, Abdel-Latif A, Rahbi H, et al. A systematic review of population-based studies of infective endocarditis. *Chest*. 2007;132:1025–35.
41. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation*. 1997;95:2098–107.
42. Lalani T, Chu VH, Park LP, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med*. 2013;173:1495–504.
43. Nagpal A, Sohail MR, Steckelberg JM. Prosthetic valve endocarditis: state of the heart. *Clin Invest*. 2012;2:803–17.
44. Jault F, Gandjbakhch I, Rama A, et al. Active native valve endocarditis: determinants of operative death and late mortality. *Ann Thorac Surg*. 1997;63:1737–41.
45. Hasbun R, Vikram HR, Barakat LA, et al. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *JAMA*. 2003;289:1933–40.
46. Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. *JAMA*. 2011;306:2239–47.
47. Tornos P, Sanz E, Permyer-Miralda G, et al. Late prosthetic valve endocarditis. Immediate and long-term prognosis. *Chest*. 1992;101:37–41.
48. Gordon SM, Serkey JM, Longworth DL, et al. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience 1992–1997. *Ann Thorac Surg*. 2000;69:1388–92.
49. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? *Circulation*. 2010;121:1141–52.
50. Funakoshi S, Kaji S, Yamamoto A, et al. Impact of early surgery in the active phase on long-term outcomes in left-sided native valve infective endocarditis. *J Thorac Cardiovasc Surg*. 2011;142:836–42.e1.
51. Bauernschmitt R, Jakob HG, Vahl CF, et al. Operation for infective endocarditis: results after implantation of mechanical valves. *Ann Thorac Surg*. 1998;65:359–64.
52. Musci M, Siniawski H, Pasic M, et al. Surgical therapy in patients with active infective endocarditis: seven-year single centre experience in a subgroup of 255 patients treated with the Shelhigh stentless bioprosthesis. *Eur J Cardiothorac Surg*. 2008;34:410–7.
53. Yu VL, Fang GD, Keys TF, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. *Ann Thorac Surg*. 1994;58:1073–7.
54. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–73.
55. Remadi JP, Habib G, Nadjji G, et al. Predictors of death and impact of surgery in *Staphylococcus aureus* infective endocarditis. *Ann Thorac Surg*. 2007;83:1295–302.
56. Hill EE, Herijgers P, Claus P, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. *Eur Heart J*. 2007;28:196–203.
57. Aksoy O, Sexton DJ, Wang A, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. *Clin Infect Dis*. 2007;44:364–72.
58. Ellis ME, Al-Abdely H, Sandridge A, et al. Fungal endocarditis: evidence in the world literature, 1965–1995. *Clin Infect Dis*. 2001;32:50–62.
59. Wolff M, Witzchitz S, Chastang C, et al. Prosthetic valve endocarditis in the ICU. Prognostic factors of overall survival in a series of 122 cases and consequences for treatment decision. *Chest*. 1995;108:688–94.
60. Chirouze C, Cabell CH, Fowler VG Jr, et al. Prognostic factors in 61 cases of *Staphylococcus aureus* prosthetic valve infective endocarditis from the International Collaboration on Endocarditis merged database. *Clin Infect Dis*. 2004;38:1323–7.
61. Melgar GR, Nasser RM, Gordon SM, et al. Fungal prosthetic valve endocarditis in 16 patients. An 11-year experience in a tertiary care hospital. *Medicine (Baltimore)*. 1997;76:94–103.
62. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005;293:3012–21.
63. Miro JM, Anguera I, Cabell CH, et al. *Staphylococcus aureus* native valve infective endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. *Clin Infect Dis*. 2005;41:507–14.
64. Hill EE, Peetermans WE, Vanderschueren S, et al. Methicillin-resistant versus methicillin-sensitive *Staphylococcus aureus* infective endocarditis. *Eur J Clin Microbiol Infect Dis*. 2008;27:445–50.
65. Attaran S, Chukwuemeka A, Punjabi PP, et al. Do all patients with prosthetic valve endocarditis need surgery? *Interact Cardiovasc Thorac Surg*. 2012;15:1057–61.
66. Cowgill LD, Addonizio VP, Hopeman AR, et al. A practical approach to prosthetic valve endocarditis. *Ann Thorac Surg*. 1987;43:450–7.
67. Ribera E, Gómez-Jiménez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med*. 1996;125:969–74.

12.4. Intervention

1. Erba PA, Habib G, Glaudemans AWJM, et al. The round table approach in infective endocarditis & cardiovascular implantable electronic devices infections: make your e-Team come true. *Eur J Nucl Med Mol Imaging*. 2017;44:1107–8.
2. Chirillo F, Scotton P, Rocco F, et al. Impact of a multidisciplinary management strategy on the outcome of patients with native valve infective endocarditis. *Am J Cardiol*. 2013;112:1171–6.
3. Botelho-Nevers E, Thuny F, Casalta JP, et al. Dramatic reduction in infective endocarditis-related mortality with a management-based approach. *Arch Intern Med*. 2009;169:1290–8.
4. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. *Lancet*. 2012;379:965–75.
5. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified risk scoring system. *J Thorac Cardiovasc Surg*. 2011;141:98–106.e1–2.
6. Sambola A, Fernández-Hidalgo N, Almirante B, et al. Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. *Am J Cardiol*. 2010;106:92–8.
7. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297:1354–61.
8. Lalani T, Chu VH, Park LP, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med*. 2013;173:1495–504.

34. Rabkin DG, Mokadam NA, Miller DW, et al. Long-term outcome for the surgical treatment of infective endocarditis with a focus on intravenous drug users. *Ann Thorac Surg*. 2012;93:51–7.
35. Hubbell G, Cheitlin MD, Rapaport E. Presentation, management, and follow-up evaluation of infective endocarditis in drug addicts. *Am Heart J*. 1981;102:85–94.
36. Wang K, Gobel F, Gleason DF, et al. Complete heart block complicating bacterial endocarditis. *Circulation*. 1972;46:939–47.
37. Middlemost S, Wisenbaugh T, Meyerowitz C, et al. A case for early surgery in native left-sided endocarditis complicated by heart failure: results in 203 patients. *J Am Coll Cardiol*. 1991;18:663–7.
38. Chan K-L. Early clinical course and long-term outcome of patients with infective endocarditis complicated by perivalvular abscess. *CMAJ*. 2002;167:19–24.
39. Jault F, Gandjbakhch I, Chastre JC, et al. Prosthetic valve endocarditis with ring abscesses. Surgical management and long-term results. *J Thorac Cardiovasc Surg*. 1993;105:1106–13.
40. Anguera I, Miro JM, Vilacosta I, et al. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. *Eur Heart J*. 2005;26:288–97.
41. Habib G, Avierinos J-F, Thuny F. Aortic valve endocarditis: is there an optimal surgical timing? *Curr Opin Cardiol*. 2007;22:77–83.
42. Spiliopoulos K, Haschemi A, Fink G, et al. Infective endocarditis complicated by paravalvular abscess: a surgical challenge. An 11-year single center experience. *Heart Surg Forum*. 2010;13:E67–73.
43. d'Udekem Y, David TE, Feindel CM, et al. Long-term results of operation for paravalvular abscess. *Ann Thorac Surg*. 1996;62:48–53.
44. Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. *J Thorac Cardiovasc Surg*. 2010;139:887–93.
45. Klieverik LMA, Yacoub MH, Edwards S, et al. Surgical treatment of active native aortic valve endocarditis with allografts and mechanical prostheses. *Ann Thorac Surg*. 2009;88:1814–21.
46. Hill EE, Herijgers P, Claus P, et al. Abscess in infective endocarditis: the value of transesophageal echocardiography and outcome: a 5-year study. *Am Heart J*. 2007;154:923–8.
47. Manne MB, Shrestha NK, Lytle BW, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. *Ann Thorac Surg*. 2012;93:489–93.
48. Head SJ, Mokhles MM, Osnabrugge RLJ, et al. Surgery in current therapy for infective endocarditis. *Vasc Health Risk Manag*. 2011;7:255–63.
49. Narducci ML, Pelargonio G, Russo E, et al. Usefulness of intracardiac echocardiography for the diagnosis of cardiovascular implantable electronic device-related endocarditis. *J Am Coll Cardiol*. 2013;61:1398–405.
50. Sohail MR, Usman DZ, Khan AH, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc*. 2008;83:46–53.
51. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727–35.
52. Rundström H, Kennergren C, Andersson R, et al. Pacemaker endocarditis during 18 years in Göteborg. *Scand J Infect Dis*. 2004;36:674–9.
53. Ho H-H, Siu C-W, Yiu K-H, et al. Prosthetic valve endocarditis in a multicenter registry of Chinese patients. *Asian Cardiovasc Thorac Ann*. 2010;18:430–4.
54. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;121:458–77.
55. Viganego F, O'Donoghue S, Eldadah Z, et al. Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol*. 2012;109:1466–71.
56. Rudasill SE, Sanaia Y, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. *J Am Coll Cardiol*. 2019;73:559–70.
57. Rodger L, Glockler-Lauff SD, Shojaei E, et al. Clinical characteristics and factors associated with mortality in first-episode infective endocarditis among persons who inject drugs. *JAMA Netw Open*. 2018;1:e185220.
58. Schranz AJ, Fleischauer A, Chu VH, et al. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170:31–40.
59. Rosenthal ES, Karchmer AW, Theisen-Toupal J, et al. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med*. 2016;129:481–5.
60. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med*. 2014;174:1369–76.
61. Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366:2466–73.
62. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation*. 2005;112:69–75.
63. Mügge A, Daniel WG, Frank G, et al. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol*. 1989;14:631–8.
64. Rohmann S, Erbel R, Darius H, et al. Prediction of rapid versus prolonged healing of infective endocarditis by monitoring vegetation size. *J Am Soc Echocardiogr*. 1991;4:465–74.
65. Habib G. Embolic risk in subacute bacterial endocarditis: determinants and role of transesophageal echocardiography. *Curr Infect Dis Rep*. 2005;7:264–71.
66. Truninger K, Attenhofer Jost CH, Seifert B, et al. Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone? *Heart*. 1999;82:714–20.
67. Fosbol EL, Park LP, Chu VH, et al. The association between vegetation size and surgical treatment on 6-month mortality in left-sided infective endocarditis. *Eur Heart J*. 2019;40:2243–51.
68. Suzuki M, Takanashi S, Ohshima Y, et al. Critical potential of early cardiac surgery for infective endocarditis with cardio-embolic strokes. *Int J Cardiol*. 2017;227:222–4.
69. García-Borbolla Fernández R, Sancho Jaldón M, Calle Pérez G, et al. Percutaneous treatment of mitral valve periprosthetic leakage. An alternative to high-risk surgery? *Rev Esp Cardiol*. 2009;62:438–41.
70. Nietlispach F, Johnson M, Moss RR, et al. Transcatheter closure of paravalvular defects using a purpose-specific occluder. *JACC Cardiovasc Interv*. 2010;3:759–65.
71. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation*. 1997;95:2098–107.
72. Baddour LM, Cha Y-M, Wilson WR. Clinical practice. Infections of cardiovascular implantable electronic devices. *N Engl J Med*. 2012;367:842–9.
73. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162:90–4.
74. Ghoreishi M, Foster N, Pasrija C, et al. Early operation in patients with mitral valve infective endocarditis and acute stroke is safe. *Ann Thorac Surg*. 2018;105:69–75.

13. PREGNANCY AND VHD

13.1. Initial Management of Women With VHD Before and During Pregnancy

1. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165–241.
2. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation*. 2001;104:515–21.
3. Elkayam U, Bitar F. Valvular heart disease and pregnancy part I: native valves. *J Am Coll Cardiol*. 2005;46:223–30.
4. Leśniak-Sobielga A, Tracz W, Kostkiewicz M, et al. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases—maternal and fetal outcome. *Int J Cardiol*. 2004;94:15–23.
5. Ducas RA, Javier DA, D'Souza R, et al. Pregnancy outcomes in women with significant valve disease: a systematic review and meta-analysis. *Heart*. 2020;106:512–9.
6. Orwat S, Diller G-P, van Hagen IM, et al. Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC registry. *J Am Coll Cardiol*. 2016;68:1727–37.
7. Roos-Hesselink J, Baris L, Johnson M, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J*. 2019;40:3848–55.
8. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac

- Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18:1119–28.
9. Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. *J Am Coll Cardiol*. 2018;71:2419–30.
 10. Thomas E, Yang J, Xu J, et al. Pulmonary hypertension and pregnancy outcomes: insights from the national inpatient sample. *J Am Heart Assoc*. 2017;6:e006144.
 11. Sugishita Y, Ito I, Kubo T. Pregnancy in cardiac patients: possible influence of volume overload by pregnancy on pulmonary circulation. *Jpn Circ J*. 1986;50:376–83.
 12. van Hagen IM, Thorne SA, Taha N, et al. Pregnancy outcomes in women with rheumatic mitral valve disease: results from the Registry of Pregnancy and Cardiac Disease. *Circulation*. 2018;137:806–16.
 13. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112:1377–82.
 14. Maréchaux S, Hachicha Z, Belloin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 2010;31:1390–7.
 15. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–13.
 2. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation*. 2001;104:515–21.
 3. Hameed A, Karaalp IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol*. 2001;37:893–9.
 4. Barbosa PJ, Lopes AA, Feitosa GS, et al. Prognostic factors of rheumatic mitral stenosis during pregnancy and puerperium. *Arq Bras Cardiol*. 2000;75:215–24.
 5. Bhatla N, Lal S, Behera G, et al. Cardiac disease in pregnancy. *Int J Gynaecol Obstet*. 2003;82:153–9.
 6. Orwat S, Diller G-P, van Hagen IM, et al. Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC registry. *J Am Coll Cardiol*. 2016;68:1727–37.
 7. Tzemos N, Silversides CK, Colman JM, et al. Late cardiac outcomes after pregnancy in women with congenital aortic stenosis. *Am Heart J*. 2009;157:474–80.
 8. Arias F, Pineda J. Aortic stenosis and pregnancy. *J Reprod Med*. 1978;20:229–32.
 9. Silversides CK, Colman JM, Sermer M, et al. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol*. 2003;91:1386–9.
 10. Yap S-C, Drenthen W, Pieper PG, et al. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol*. 2008;126:240–6.
 11. Sugishita Y, Ito I, Kubo T. Pregnancy in cardiac patients: possible influence of volume overload by pregnancy on pulmonary circulation. *Jpn Circ J*. 1986;50:376–83.
 12. Bryg RJ, Gordon PR, Kudesia VS, et al. Effect of pregnancy on pressure gradient in mitral stenosis. *Am J Cardiol*. 1989;63:384–6.
 13. Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and post-valvuloplasty variables that predict long-term outcome. *Circulation*. 2002;105:1465–71.
 14. van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132:132–42.
 15. De Santo LS, Romano G, Della Corte A, et al. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation, a pilot observational study on a comprehensive pre-operative counseling protocol. *J Am Coll Cardiol*. 2012;59:1110–5.
 16. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165–241.

13.1.1. Medical Therapy for Women With VHD Before and During Pregnancy

1. Elkayam U, Bitar F. Valvular heart disease and pregnancy part I: native valves. *J Am Coll Cardiol*. 2005;46:223–30.
2. al Kasab SM, Sabag T, al Zaibag M, et al. Beta-adrenergic receptor blockade in the management of pregnant women with mitral stenosis. *Am J Obstet Gynecol*. 1990;163:37–40.
3. Nakhjavan FK, Katz MR, Maranhao V, et al. Analysis of influence of catecholamine and tachycardia during supine exercise in patients with mitral stenosis and sinus rhythm. *Br Heart J*. 1969;31:753–61.
4. Bhatia ML, Shrivastava S, Roy SB. Immediate haemodynamic effects of a beta adrenergic blocking agent-propranolol in mitral stenosis at fixed heart rates. *Br Heart J*. 1972;34:638–44.
5. Lydakis C, Lip GY, Beevers M, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens*. 1999;12:541–7.
6. Ruys TP, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. *Int J Cardiol*. 2014;177:124–8.
7. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165–241.
8. Taylor J. The first ESC guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;32:3055–6.
9. Schaefer C. Angiotensin II-receptor-antagonists: further evidence of fetotoxicity but not teratogenicity. *Birth Defects Res Part A Clin Mol Teratol*. 2003;67:591–4.
10. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443–51.
11. Shotan A, Widerhorn J, Hurst A, et al. Risks of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med*. 1994;96:451–6.
12. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–104.
13. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Developed in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–51.

13.1.2. Intervention for Women With Native VHD Before and During Pregnancy

13.1.2.1. Pre-Pregnancy Intervention

1. Leśniak-Sobielga A, Tracz W, Kostkiewicz M, et al. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases—maternal and fetal outcome. *Int J Cardiol*. 2004;94:15–23.

13.1.2.2. During-Pregnancy Intervention

1. Tzemos N, Silversides CK, Colman JM, et al. Late cardiac outcomes after pregnancy in women with congenital aortic stenosis. *Am Heart J*. 2009;157:474–80.
2. Banning AP, Pearson JF, Hall RJ. Role of balloon dilatation of the aortic valve in pregnant patients with severe aortic stenosis. *Br Heart J*. 1993;70:544–5.
3. Easterling TR, Chadwick HS, Otto CM, et al. Aortic stenosis in pregnancy. *Obstet Gynecol*. 1988;72:113–8.
4. Lao TT, Adelman AG, Sermer M, et al. Balloon valvuloplasty for congenital aortic stenosis in pregnancy. *Br J Obstet Gynaecol*. 1993;100:1141–2.
5. McIvor RA. Percutaneous balloon aortic valvuloplasty during pregnancy. *Int J Cardiol*. 1991;32:1–3.
6. Myerson SG, Mitchell ARJ, Ormerod OJM, et al. What is the role of balloon dilatation for severe aortic stenosis during pregnancy? *J Heart Valve Dis*. 2005;14:147–50.
7. Tumelero RT, Duda NT, Tognon AP, et al. Percutaneous balloon aortic valvuloplasty in a pregnant adolescent. *Arq Bras Cardiol*. 2004;82:98–101.
8. McCann GP, Steadman CD, Ray SG, et al. Managing the asymptomatic patient with severe aortic stenosis: randomised controlled trials of early surgery are overdue. *Heart*. 2011;97:1119–21.
9. Ben Farhat M, Gamra H, Betbout F, et al. Percutaneous balloon mitral commissurotomy during pregnancy. *Heart*. 1997;77:564–7.
10. de Souza JA, Martinez EE Jr, Ambrose JA, et al. Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. *J Am Coll Cardiol*. 2001;37:900–3.

11. Glantz JC, Pomerantz RM, Cunningham MJ, et al. Percutaneous balloon valvuloplasty for severe mitral stenosis during pregnancy: a review of therapeutic options. *Obstet Gynecol Surv.* 1993;48:503–8.
12. Iung B, Cormier B, Elias J, et al. Usefulness of percutaneous balloon commissurotomy for mitral stenosis during pregnancy. *Am J Cardiol.* 1994;73:398–400.
13. Weiss BM, von Segesser LK, Alon E, et al. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984–1996. *Am J Obstet Gynecol.* 1998;179:1643–53.
14. Becker RM. Intracardiac surgery in pregnant women. *Ann Thorac Surg.* 1983;36:453–8.
15. Chambers CE, Clark SL. Cardiac surgery during pregnancy. *Clin Obstet Gynecol.* 1994;37:316–23.
16. Parry AJ, Westaby S. Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg.* 1996;61:1865–9.
17. Gulraze A, Kurdi W, Niaz F, et al. Mitral balloon valvuloplasty during pregnancy: the long term up to 17 years obstetric outcome and childhood development. *Pak J Med Sci.* 2014;30:86–90.
18. Vinayakumar D, Vinod GV, Madhavan S, et al. Maternal and fetal outcomes in pregnant women undergoing balloon mitral valvotomy for rheumatic mitral stenosis. *Indian Heart J.* 2016;68:780–2.
19. Salome N, Dias CC, Ribeiro J, et al. Balloon mitral valvuloplasty during pregnancy—our experience. *Rev Port Cardiol.* 2002;21:1437–44.
20. Weiss BM, von Segesser LK, Alon E, et al. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984–1996. *Am J Obstet Gynecol.* 1998;179:1643–53.

13.2. Prosthetic Valves in Pregnant Women

13.2.1. Initial Management

1. Samiei N, Amirsardari M, Rezaei Y, et al. Echocardiographic evaluation of hemodynamic changes in left-sided heart valves in pregnant women with valvular heart disease. *Am J Cardiol.* 2016;118:1046–52.
 2. Goland S, Schwartzberg S, Fan J, et al. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? *J Cardiovasc Pharmacol Ther.* 2014;19:451–6.
 3. Vause S, Clarke B, Tower CL, et al. Pregnancy outcomes in women with mechanical prosthetic heart valves: a prospective descriptive population based study using the United Kingdom Obstetric Surveillance System (UKOSS) data collection system. *BJOG.* 2017;124:1411–9.
 4. van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation.* 2015;132:132–42.
 5. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J.* 2017;38:1509–16.
 6. Steinberg ZL, Dominguez-Islas CP, Otto CM, et al. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. *J Am Coll Cardiol.* 2017;69:2681–91.
 7. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:589–90.
 8. Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *J Am Coll Cardiol.* 2004;43:77–84.
 9. Özkan M, Çakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation.* 2013;128:532–40.
 10. Alshawabkeh L, Economy KE, Valente AM. Anticoagulation during pregnancy: evolving strategies with a focus on mechanical valves. *J Am Coll Cardiol.* 2016;68:1804–13.
 11. Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *J Am Coll Cardiol.* 2004;43:77–84.
 12. Ozkan M, Cakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation.* 2013;128:532–40.
- ### 13.2.2. Anticoagulation for Pregnant Women With Mechanical Prosthetic Heart Valves
1. Alshawabkeh L, Economy KE, Valente AM. Anticoagulation during pregnancy: evolving strategies with a focus on mechanical valves. *J Am Coll Cardiol.* 2016;68:1804–13.
 2. Samiei N, Amirsardari M, Rezaei Y, et al. Echocardiographic evaluation of hemodynamic changes in left-sided heart valves in pregnant women with valvular heart disease. *Am J Cardiol.* 2016;118:1046–52.
 3. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J.* 2017;38:1509–16.
 4. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med.* 2000;160:191–6.
 5. Lawley CM, Lain SJ, Algert CS, et al. Prosthetic heart valves in pregnancy, outcomes for women and their babies: a systematic review and meta-analysis. *BJOG.* 2015;122:1446–55.
 6. Xu Z, Fan J, Luo X, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. *Can J Cardiol.* 2016;32:1248.e1–9.
 7. Batra J, Itagaki S, Egorova NN, et al. Outcomes and long-term effects of pregnancy in women with biologic and mechanical valve prostheses. *Am J Cardiol.* 2018;122:1738–44.
 8. Yinon Y, Siu SC, Warshafsky C, et al. Use of low molecular weight heparin in pregnant women with mechanical heart valves. *Am J Cardiol.* 2009;104:1259–63.
 9. Rowan JA, McCowan LM, Raudkivi PJ, et al. Enoxaparin treatment in women with mechanical heart valves during pregnancy. *Am J Obstet Gynecol.* 2001;185:633–7.
 10. Abildgaard U, Sandset PM, Hammerstrøm J, et al. Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin. *Thromb Res.* 2009;124:262–7.
 11. van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation.* 2015;132:132–42.
 12. Goland S, Schwartzberg S, Fan J, et al. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? *J Cardiovasc Pharmacol Ther.* 2014;19:451–6.
 13. Elkayam U. Anticoagulation therapy for pregnant women with mechanical prosthetic heart valves: how to improve safety? *J Am Coll Cardiol.* 2017;69:2692–5.
 14. Vause S, Clarke B, Tower CL, et al. Pregnancy outcomes in women with mechanical prosthetic heart valves: a prospective descriptive population based study using the United Kingdom Obstetric Surveillance System (UKOSS) data collection system. *BJOG.* 2017;124:1411–9.
 15. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. *Thromb Haemost.* 2004;92:747–51.
 16. Steinberg ZL, Dominguez-Islas CP, Otto CM, et al. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. *J Am Coll Cardiol.* 2017;69:2681–91.
 17. D'Souza R, Silversides CK, McLintock C. Optimal anticoagulation for pregnant women with mechanical heart valves. *Semin Thromb Hemost.* 2016;42:798–804.
 18. Vitale N, De Feo M, De Santo LS, et al. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol.* 1999;33:1637–41.
 19. Meschengieser SS, Fondevila CG, Santarelli MT, et al. Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart.* 1999;82:23–6.
 20. Sadler L, McCowan L, White H, et al. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG.* 2000;107:245–53.
 21. Horlocker TT, Vandermeulen E, Kopp SL, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (fourth edition). *Reg Anesth Pain Med.* 2018;43:263–309.
 22. De Santo LS, Romano G, Della Corte A, et al. Mitral mechanical replacement in young rheumatic women: analysis of long-term survival,

valve-related complications, and pregnancy outcomes over a 3707-patient-year follow-up. *J Thorac Cardiovasc Surg.* 2005;130:13–9.

23. Ayad SW, Hassanein MM, Mohamed EA, et al. Maternal and fetal outcomes in pregnant women with a prosthetic mechanical heart valve. *Clin Med Insights Cardiol.* 2016;10:11–7.
24. Al-Lawati AAM, Venkitraman M, Al-Delaime T, et al. Pregnancy and mechanical heart valves replacement; dilemma of anticoagulation. *Eur J Cardiothorac Surg.* 2002;22:223–7.
25. Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: a meta-analysis. *Interact Cardiovasc Thorac Surg.* 2014;18:797–806.
26. Özkan M, Çakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation.* 2013;128:532–40.
27. McLintock C, McCowan LME, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG.* 2009;116:1585–92.
28. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev.* 2013;CD003464.
29. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369:1206–14.
30. Lameijer H, Aalberts JJJ, van Veldhuisen DJ, et al. Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review. *Thromb Res.* 2018;169:123–7.
31. Beyer-Westendorf J, Michalski F, Tittel L, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. *Thromb Haemost.* 2016;116:651–8.
32. Cohen H, Arachchillage DR, Middeldorp S, et al. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2016;14:1673–6.
33. Quinn J, Von Klemperer K, Brooks R, et al. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. *Haematologica.* 2009;94:1608–12.
34. James AH, Brancizio LR, Gehrig TR, et al. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. *J Matern Fetal Neonatal Med.* 2006;19:543–9.
35. Meschengieser SS, Fondevila CG, Santarelli MT, et al. Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart.* 1999;82:23–6.
36. De Santo LS, Romano G, Della Corte A, et al. Mitral mechanical replacement in young rheumatic women: analysis of long-term survival, valve-related complications, and pregnancy outcomes over a 3707-patient-year follow-up. *J Thorac Cardiovasc Surg.* 2005;130:13–9.
37. Al-Lawati AA, Venkitraman M, Al-Delaime T, et al. Pregnancy and mechanical heart valves replacement; dilemma of anticoagulation. *Eur J Cardiothorac Surg.* 2002;22:223–7.
38. De Santo LS, Romano G, Della Corte A, et al. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation, a pilot observational study on a comprehensive pre-operative counseling protocol. *J Am Coll Cardiol.* 2012;59:1110–5.
39. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG.* 2009;116:1585–92.
40. Sillesen M, Hjortdal V, Vejstrup N, et al. Pregnancy with prosthetic heart valves—30 years' nationwide experience in Denmark. *Eur J Cardiothorac Surg.* 2011;40:448–54.
41. James AH, Brancizio LR, Gehrig TR, et al. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. *J Matern Fetal Neonatal Med.* 2006;19:543–9.
42. Salazar E, Izaguirre R, Verdejo J, et al. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. *J Am Coll Cardiol.* 1996;27:1698–703.
43. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J.* 1994;71:196–201.
44. Ozkan M, Çakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation.* 2013;128:532–40.
45. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369:1206–14.

14. SURGICAL CONSIDERATIONS

14.1. Evaluation and Management of CAD in Patients With VHD

14.1.1. Management of CAD in Patients Undergoing TAVI

1. Bajaj A, Pancholy S, Sethi A, et al. Safety and feasibility of PCI in patients undergoing TAVR: a systematic review and meta-analysis. *Heart Lung.* 2017;46:92–9.
2. Chakravarty T, Sharma R, Abramowitz Y, et al. Outcomes in patients with transcatheter aortic valve replacement and left main stenting: the TAVR-LM registry. *J Am Coll Cardiol.* 2016;67:951–60.
3. Mohr FW, Morice M-C, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629–38.
4. Thalji NM, Suri RM, Daly RC, et al. The prognostic impact of concomitant coronary artery bypass grafting during aortic valve surgery: implications for revascularization in the transcatheter era. *J Thorac Cardiovasc Surg.* 2015;149:451–60.
5. Faroux L, Guimaraes L, Wintzer-Wehekind J, et al. Coronary artery disease and transcatheter aortic valve replacement: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;74:362–72.
6. Goel SS, Ige M, Tuzcu EM, et al. Severe aortic stenosis and coronary artery disease—implications for management in the transcatheter aortic valve replacement era: a comprehensive review. *J Am Coll Cardiol.* 2013;62:1–10.
7. Sankaramangalam K, Banerjee K, Kandregula K, et al. Impact of coronary artery disease on 30-day and 1-year mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis. *J Am Heart Assoc.* 2017;6:e006092.
8. Millan-Iturbide O, Sawaya FJ, Lønborg J, et al. Coronary artery disease, revascularization, and clinical outcomes in transcatheter aortic valve replacement: real-world results from the East Denmark Heart Registry. *Catheter Cardiovasc Interv.* 2018;92:818–26.
9. Witberg G, Regev E, Chen S, et al. The prognostic effects of coronary disease severity and completeness of revascularization on mortality in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2017;10:1428–35.
10. Chieffo A, Giustino G, Spagnolo P, et al. Routine screening of coronary artery disease with computed tomographic coronary angiography in place of invasive coronary angiography in patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Interv.* 2015;8:e002025.
11. Rossi A, De Cecco CN, Kennon SRO, et al. CT angiography to evaluate coronary artery disease and revascularization requirement before transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr.* 2017;11:338–46.
12. van den Boogert TPW, Vendrik J, Claessen B, et al. CTCA for detection of significant coronary artery disease in routine TAVI work-up: A systematic review and meta-analysis. *Neth Heart J.* 2018;26:591–9.
13. Pesarini G, Scarsini R, Zivelonghi C, et al. Functional assessment of coronary artery disease in patients undergoing transcatheter aortic valve implantation: influence of pressure overload on the evaluation of lesions severity. *Circ Cardiovasc Interv.* 2016;9:e004088.
14. Ahmad Y, Götzberg M, Cook C, et al. Coronary hemodynamics in patients with severe aortic stenosis and coronary artery disease undergoing transcatheter aortic valve replacement: implications for clinical indices of coronary stenosis severity. *JACC Cardiovasc Interv.* 2018;11:2019–31.
15. Yamanaka F, Shishido K, Ochiai T, et al. Instantaneous wave-free ratio for the assessment of intermediate coronary artery stenosis in patients with severe aortic valve stenosis: comparison with myocardial perfusion scintigraphy. *JACC Cardiovasc Interv.* 2018;11:2032–40.

14.1.2. Management of CAD in Patients Undergoing Valve Surgery

1. Graboyes TB, Cohn PF. The prevalence of angina pectoris and abnormal coronary arteriograms in severe aortic valvular disease. *Am Heart J.* 1977;93:683–6.
2. Ramsdale DR, Bennett DH, Bray CL, et al. Angina, coronary risk factors and coronary artery disease in patients with valvular disease. A prospective study. *Eur Heart J.* 1984;5:716–26.

3. Dangas G, Khan S, Curry BH, et al. Angina pectoris in severe aortic stenosis. *Cardiology*. 1999;92:1–3.
4. Basta LL, Raines D, Najjar S, et al. Clinical, haemodynamic, and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. *Br Heart J*. 1975;37:150–7.
5. Thalji NM, Suri RM, Daly RC, et al. Assessment of coronary artery disease risk in 5463 patients undergoing cardiac surgery: when is preoperative coronary angiography necessary? *J Thorac Cardiovasc Surg*. 2013;146:1055–63, 64.e1.
6. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol*. 1976;38:46–51.
7. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300:1350–8.
8. Heidenreich PA, Kapoor JR. Radiation induced heart disease: systemic disorders in heart disease. *Heart*. 2009;95:252–8.
9. Gahl K, Sutton R, Pearson M, et al. Mitral regurgitation in coronary heart disease. *Br Heart J*. 1977;39:13–8.
10. Enriquez-Sarano M, Klotas E, Garratt KN, et al. Secular trends in coronary atherosclerosis—analysis in patients with valvular regurgitation. *N Engl J Med*. 1996;335:316–22.
11. Breisblatt WM, Cerqueira M, Francis CK, et al. Left ventricular function in ischemic mitral regurgitation—a precatheterization assessment. *Am Heart J*. 1988;115:77–82.
12. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol*. 2010;55:2663–99.
13. Opolski MP, Kim WK, Liebetrau C, et al. Diagnostic accuracy of computed tomography angiography for the detection of coronary artery disease in patients referred for transcatheter aortic valve implantation. *Clin Res Cardiol*. 2015;104:471–80.
14. Hamdan A, Wellnhofer E, Konen E, et al. Coronary CT angiography for the detection of coronary artery stenosis in patients referred for transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr*. 2015;9:31–41.
15. Andreini D, Pontone G, Mushtaq S, et al. Diagnostic accuracy of multidetector computed tomography coronary angiography in 325 consecutive patients referred for transcatheter aortic valve replacement. *Am Heart J*. 2014;168:332–9.
16. Chieffo A, Giustino G, Spagnolo P, et al. Routine screening of coronary artery disease with computed tomographic coronary angiography in place of invasive coronary angiography in patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2015;8:e002025.
17. Matsumoto S, Yamada Y, Hashimoto M, et al. CT imaging before transcatheter aortic valve implantation (TAVI) using variable helical pitch scanning and its diagnostic performance for coronary artery disease. *Eur Radiol*. 2017;27:1963–70.
18. Rossi A, De Cecco CN, Kennon SRO, et al. CT angiography to evaluate coronary artery disease and revascularization requirement before trans-catheter aortic valve replacement. *J Cardiovasc Comput Tomogr*. 2017;11:338–46.
19. Thalji NM, Suri RM, Daly RC, et al. The prognostic impact of concomitant coronary artery bypass grafting during aortic valve surgery: implications for revascularization in the transcatheter era. *J Thorac Cardiovasc Surg*. 2015;149:451–60.
20. Byrne JG, Leacche M, Vaughan DE, et al. Hybrid cardiovascular procedures. *JACC Cardiovasc Interv*. 2008;1:459–68.
21. Pontone G, Andreini D, Bartorelli AL, et al. Feasibility and accuracy of a comprehensive multidetector computed tomography acquisition for patients referred for balloon-expandable transcatheter aortic valve implantation. *Am Heart J*. 2011;161:1106–13.
22. Lund O, Nielsen TT, Pilegaard HK, et al. The influence of coronary artery disease and bypass grafting on early and late survival after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg*. 1990;100:327–37.
23. Beach JM, Mihaljevic T, Svensson LG, et al. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol*. 2013;61:837–48.
24. Badhwar V, Rankin JS, Damiano RJ Jr, et al. The Society of Thoracic Surgeons 2017 clinical practice guidelines for the surgical treatment of atrial fibrillation. *Ann Thorac Surg*. 2017;103:329–41.
25. Ad N, Holmes SD, Pritchard G, et al. Association of operative risk with the outcome of concomitant Cox Maze procedure: a comparison of results across risk groups. *J Thorac Cardiovasc Surg*. 2014;148:3027–33.
26. Ad N, Holmes SD, Rongione AJ, et al. The long-term safety and efficacy of concomitant Cox maze procedures for atrial fibrillation in patients without mitral valve disease. *J Thorac Cardiovasc Surg*. 2019;157:1505–14.
27. Gillinov AM, Bakaeen F, McCarthy PM, et al. Surgery for paroxysmal atrial fibrillation in the setting of mitral valve disease: a role for pulmonary vein isolation? *Ann Thorac Surg*. 2006;81:19–26.
28. Gillinov AM, Gelijns AC, Parides MK, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*. 2015;372:1399–409.
29. Abreu Filho CA, Lisboa LA, Dallan LA, et al. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation*. 2005;112:120–5.
30. Akpinar B, Guden M, Sagbas E, et al. Combined radiofrequency modified maze and mitral valve procedure through a port access approach: early and mid-term results. *Eur J Cardiothorac Surg*. 2003;24:223–30.
31. Chua YL, Schaff HV, Orszulak TA, et al. Outcome of mitral valve repair in patients with preoperative atrial fibrillation. Should the maze procedure be combined with mitral valvuloplasty? *J Thorac Cardiovasc Surg*. 1994;107:408–15.
32. Deneke T, Khargi K, Grewe PH, et al. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J*. 2002;23:558–66.
33. Jessurun ER, van Hemel NM, Defauw JJ, et al. A randomized study of combining maze surgery for atrial fibrillation with mitral valve surgery. *J Cardiovasc Surg (Torino)*. 2003;44:9–18.
34. Rankin JS, Grau-Sepulveda MV, Ad N, et al. Associations between surgical ablation and operative mortality after mitral valve procedures. *Ann Thorac Surg*. 2018;105:1790–6.
35. Ad N, Holmes SD, Lamont D, et al. Left-sided surgical ablation for patients with atrial fibrillation who are undergoing concomitant cardiac surgical procedures. *Ann Thorac Surg*. 2017;103:58–65.
36. Huffman MD, Karmali KN, Berendsen MA, et al. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev*. 2016;CD011814.
37. Huffman MD, Malaisrie SC, Karmali KN. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *JAMA Cardiol*. 2017;2:334–5.
38. Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. 2018;319:365–74.
39. Yao X, Gersh BJ, Holmes DR Jr, et al. Association of surgical left atrial appendage occlusion with subsequent stroke and mortality among patients undergoing cardiac surgery. *JAMA*. 2018;319:2116–26.
40. Johnsrud DO, Melduni RM, Lahr B, et al. Evaluation of anticoagulation use and subsequent stroke in patients with atrial fibrillation after empiric surgical left atrial appendage closure: A retrospective case-control study. *Clin Cardiol*. 2018;41:1578–82.
41. Abris VA, Narichania AD, Love WT, et al. Left atrial appendage exclusion during mitral valve surgery and stroke in atrial fibrillation. *J Interv Card Electrophysiol*. 2018;53:285–92.
42. García-Fernández MA, Pérez-David E, Quiles J, et al. Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 2003;42:1253–8.
43. Noseworthy PA, Yao X, Deshmukh AJ, et al. Patterns of anticoagulation use and cardioembolic risk after catheter ablation for atrial fibrillation. *J Am Heart Assoc*. 2015;4:e002597.
44. Eitel C, Koch J, Sommer P, et al. Novel oral anticoagulants in a real-world cohort of patients undergoing catheter ablation of atrial fibrillation. *Europace*. 2013;15:1587–93.
45. Melduni RM, Schaff HV, Lee H-C, et al. Impact of left atrial appendage closure during cardiac surgery on the occurrence of early postoperative atrial fibrillation, stroke, and mortality: a propensity score-matched analysis of 10 633 patients. *Circulation*. 2017;135:366–78.

14.2. Intervention for AF in Patients With VHD

1. Ad N, Henry L, Hunt S, et al. Do we increase the operative risk by adding the Cox Maze III procedure to aortic valve replacement and coronary artery bypass surgery? *J Thorac Cardiovasc Surg*. 2012;143:936–44.

15. NONCARDIAC SURGERY IN PATIENTS WITH VHD

15.1. Diagnosis of Patients With VHD Undergoing Noncardiac Surgery

1. Liu JB, Liu Y, Cohen ME, et al. Defining the intrinsic cardiac risks of operations to improve preoperative cardiac risk assessments. *Anesthesiology*. 2018;128:283–92.
2. Wijesundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet*. 2018;391:2631–40.
3. Dakik HA, Chehab O, Eldirani M, et al. A new index for pre-operative cardiovascular evaluation. *J Am Coll Cardiol*. 2019;73:3067–78.
4. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–643.
5. Douglas PS, Garcia MJ, Haines DE, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2011;24:229–67.

15.2. Management of the Symptomatic Patient

1. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e278–333.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–643.
3. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–8.
4. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2015;66:113–21.
5. Thyregod HGH, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184–94.
6. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–20.
7. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218–25.
8. Okuno T, Yahagi K, Horiuchi Y, et al. The role of transcatheter aortic valve replacement in the patients with severe aortic stenosis requiring major non-cardiac surgery. *Cardiovasc Interv Ther*. 2019;34:345–51.
9. Kogoj P, Devjak R, Bunc M. Balloon aortic valvuloplasty (BAV) as a bridge to aortic valve replacement in cancer patients who require urgent non-cardiac surgery. *Radiol Oncol*. 2014;48:62–6.
10. Calicchio F, Guarracino F, Giannini C, et al. Balloon aortic valvuloplasty before noncardiac surgery in severe aortic stenosis: a single-center experience. *J Cardiovasc Med (Hagerstown)*. 2017;18:109–13.
11. Kennon S, Archbold A. Expert opinion: guidelines for the management of patients with aortic stenosis undergoing non-cardiac surgery: out of date and overly prescriptive. *Interv Cardiol*. 2017;12:133–6.

15.3. Management of the Asymptomatic Patient

1. Agarwal S, Rajamanickam A, Bajaj NS, et al. Impact of aortic stenosis on postoperative outcomes after noncardiac surgeries. *Circ Cardiovasc Qual Outcomes*. 2013;6:193–200.
2. Zahid M, Sonel AF, Saba S, et al. Perioperative risk of noncardiac surgery associated with aortic stenosis. *Am J Cardiol*. 2005;96:436–8.
3. Tashiro T, Pislaru SV, Blustin JM, et al. Perioperative risk of major non-cardiac surgery in patients with severe aortic stenosis: a reappraisal in contemporary practice. *Eur Heart J*. 2014;35:2372–81.
4. Bajaj NS, Agarwal S, Rajamanickam A, et al. Impact of severe mitral regurgitation on postoperative outcomes after noncardiac surgery. *Am J Med*. 2013;126:529–35.
5. Lai H-C, Lai H-C, Lee W-L, et al. Mitral regurgitation complicates postoperative outcome of noncardiac surgery. *Am Heart J*. 2007;153:712–7.
6. Meyer S, McLaughlin VV, Seyfarth H-J, et al. Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey. *Eur Respir J*. 2013;41:1302–7.
7. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. *Chest*. 2019;155:565–86.
8. Lai H-C, Lai H-C, Lee W-L, et al. Impact of chronic advanced aortic regurgitation on the perioperative outcome of noncardiac surgery. *Acta Anaesthesiol Scand*. 2010;54:580–8.
9. Goertz AW, Lindner KH, Seefelder C, et al. Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. *Anesthesiology*. 1993;78:834–41.
10. Goertz AW, Lindner KH, Schütz W, et al. Influence of phenylephrine bolus administration on left ventricular filling dynamics in patients with coronary artery disease and patients with valvular aortic stenosis. *Anesthesiology*. 1994;81:49–58.
11. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e278–333.
12. Christ M, Sharkova Y, Geldner G, et al. Preoperative and perioperative care for patients with suspected or established aortic stenosis facing non-cardiac surgery. *Chest*. 2005;128:2944–53.
13. O'Keefe JHJ, Shub C, Rettke SR. Risk of noncardiac surgical procedures in patients with aortic stenosis. *Mayo Clin Proc*. 1989;64:400–5.
14. Ho MC, Beathe JC, Sharrock NE. Hypotensive epidural anesthesia in patients with aortic stenosis undergoing total hip replacement. *Reg Anesth Pain Med*. 2008;33:129–33.
15. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–643.
16. Mittnacht AJ, Fanshawe M, Konstadt S. Anesthetic considerations in the patient with valvular heart disease undergoing noncardiac surgery. *Semin Cardiothorac Vasc Anesth*. 2008;12:33–59.
17. Frogel J, Galuska D. Anesthetic considerations for patients with advanced valvular heart disease undergoing noncardiac surgery. *Anesthesiol Clin*. 2010;28:67–85.
18. Smilowitz NR, Armanious A, Bangalore S, et al. Cardiovascular outcomes of patients with pulmonary hypertension undergoing noncardiac surgery. *Am J Cardiol*. 2019;123:1532–7.

16. EVIDENCE GAPS AND FUTURE DIRECTIONS

16.1. Prevention of Valve Disease: Stage A

1. Nazarzadeh M, Pinho-Gomes A-C, Smith Byrne K, et al. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiol*. 2019;4:788–95.
2. Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016;2:16006.
3. Lindman BR. Aortic stenosis: moving from treatment to prevention. *J Am Coll Cardiol*. 2017;69:1533–5.

- Atkins SK, Aikawa E. Valve under the microscope: shining a light on emerging technologies elucidating disease mechanisms. *Heart*. 2019;105:1610–1.
- Peeters FECM, Meex SJR, Dweck MR, et al. Calcific aortic valve stenosis: hard disease in the heart: a biomolecular approach towards diagnosis and treatment. *Eur Heart J*. 2018;39:2618–24.
- Carapetis JR. Rheumatic heart disease in developing countries. *N Engl J Med*. 2007;357:439–41.
- Soler-Soler J, Galve E. Worldwide perspective of valve disease. *Heart*. 2000;83:721–5.
- Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–11.
- Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127:143–52.
- Hagler MA, Hadley TM, Zhang H, et al. TGF- β signalling and reactive oxygen species drive fibrosis and matrix remodelling in myxomatous mitral valves. *Cardiovasc Res*. 2013;99:175–84.
- Miller JD, Weiss RM, Heistad DD. Calcific aortic valve stenosis: methods, models, and mechanisms. *Circ Res*. 2011;108:1392–412.
- Lindman BR, Arnold SV, Bagur R, et al. Priorities for patient-centered research in valvular heart disease: a report from the National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e015975.

16.2. Medical Therapy to Treat or Prevent Disease Progression: Stage B

- Park SJ, Dweck MR. Multimodality imaging for the assessment of severe aortic stenosis. *J Cardiovasc Imaging*. 2019;27:235–46.
- Everett RJ, Dweck MR. Renin-angiotensin system inhibition in aortic stenosis: thinking beyond transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;74:642–4.
- Lindman BR, Otto CM, Douglas PS, et al. Blood pressure and arterial load after transcatheter aortic valve replacement for aortic stenosis. *Circ Cardiovasc Imaging*. 2017;10:e006308.

- Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–12.
- Lindman BR, Arnold SV, Bagur R, et al. Priorities for patient-centered research in valvular heart disease: a report from the National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e015975.

16.3. Optimal Timing of Intervention: Stage C

- Nicolau S, Ionescu T, Cleanoveanu G, et al. [National system for the registration of congenital malformations and genetic diseases] [Article in Romanian]. *Rev Pediatr Obstet Ginecol Pediatr*. 1987;36:193–215.
- Campo J, Tsois A, Kruse J, et al. Prognosis of severe asymptomatic aortic stenosis with and without surgery. *Ann Thorac Surg*. 2019;108:74–9.
- Kataruka A, Otto CM. Valve durability after transcatheter aortic valve implantation. *J Thorac Dis*. 2018;10:S3629–S36.
- Lindman BR, Arnold SV, Bagur R, et al. Priorities for patient-centered research in valvular heart disease: a report from the National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e015975.

16.4. Better Options for Intervention: Stage D

- Otto CM. Informed shared decisions for patients with aortic stenosis. *N Engl J Med*. 2019;380:1769–70.
- Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016;2:16006.
- Lindman BR, Arnold SV, Bagur R, et al. Priorities for patient-centered research in valvular heart disease: a report from the National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e015975.

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section
Catherine M. Otto (Co-Chair)	University of Washington—J. Ward Kennedy-Hamilton Endowed Chair in Cardiology and Professor of Medicine	None	None	None	None	None	None	None
Rick A. Nishimura (Co-Chair)	Mayo Clinic—Department of Cardiovascular Medicine and Judd and Mary Morris Leighton Professor of Cardiovascular Diseases and Hypertension	None	None	None	None	None	None	None
Robert O. Bonow	Northwestern University, Feinberg School of Medicine—Vice Chair for Development and Innovation, Department of Medicine; Max and Lilly Goldberg Distinguished Professor of Cardiology; and Professor of Medicine	None	None	None	None	None	None	None
Blase A. Carabello	East Carolina Heart Institute at East Carolina University—Professor and Chief, Division of Cardiology	None	None	None	• Edwards Lifesciences (DSMB)†	None	None	3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15
John P. Erwin III	Clinical Department Chair of Internal Medicine, NorthShore University Health System Clinical Professor, University of Chicago Pritzker School of Medicine	None	None	None	None	None	None	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section
Federico Gentile	Centro Cardiologico Gentile, Naples, Italy	None	None	None	None	None	None	None
Hani Jneid	Baylor College of Medicine—Associate Professor of Medicine; The Michael DeBakey VA Medical Center—Director of Interventional Cardiology Research	None	None	None	None	None	None	None
Eric V. Krieger	University of Washington, School of Medicine—Associate Professor of Medicine; Director, Seattle Adult Congenital Heart Disease Service	None	None	None	None	None	None	None
Michael Mack	Baylor Scott & White Health—Chair, Cardiovascular Service line	None	None	None	- Abbott Vascular† - Edwards Lifesciences† - Medtronic†	None	None	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Christopher McLeod	Mayo Clinic—Clinical Director for Cardiovascular Medicine (Jacksonville, FL)	None	None	None	None	None	None	None
Patrick T. O’Gara	Watkins Family Distinguished Chair in Cardiology, Brigham and Women’s Hospital; Professor of Medicine Harvard Medical School	None	None	None	None	- Edwards Scientific† - Medtronic	None	3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15
Vera H. Rigolin	Northwestern University, Feinberg School of Medicine—Professor of Medicine (Cardiology)	None	None	- AstraZeneca - Merck/Schering-Plough* - Pfizer*	None	None	None	3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15
Thoralf M. Sundt III	Massachusetts General Hospital—Chief, Division of Cardiac Surgery; Co-Director, Corrigan Minehan Heart Center	None	None	None	Thrasos*	- Edwards Lifesciences‡ - Medtronic‡	None	3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15
Annemarie Thompson	Duke University Medical Center—Professor of Anesthesiology, Medicine, and Population Health Sciences, Director, Anesthesiology Residency Program	None	None	None	None	None	None	None
Christopher Toly	Simulab Corporation—Chief Executive Officer, Chief Technology Officer	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the Writing Committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥\$5000 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. Please refer to <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†Significant relationship.

‡This disclosure was entered under the Clinical Trial Enroller category in ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or ACC/AHA) Disclosure Policy for Writing Committees.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; DSMB, Data and Safety Monitoring Board; FL, Florida; and VA, Veterans Affairs.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Abigail M. Khan	Official Reviewer—AHA	Oregon Health and Science University	None	None	None	None	None	None
Andrew R. Waxler	Official Reviewer—Board of Governors Alternate	Penn State Health	None	• Amarin* • Sanofi—Regeron*	None	None	• DalCor Pharmaceutical • Medicines Company • Penn State—St Joseph Medical Center Foundation Board Member† • Penn State—St. Joseph Medical Center Pharmacy and Therapeutics Committee Member† • Pfizer Inc • Regeneron • Sanofi	None
Daniel M. Shindler	Official Reviewer—ACC Board of Governors	University of Medicine and Dentistry, Robert Wood Johnson Medical School, New Brunswick, New Jersey	None	None	None	None	None	None
William A. Zoghbi	Official Reviewer—ACC Clinical Policy Approval Committee	Houston Methodist-Chairman, Department of Cardiology	None	None	None	None	None	None
Y. Joseph Woo	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	None	None	None	None	• NIH*	None
Adrian F. Hernandez	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Duke University School of Medicine	• Amgen Inc. • AstraZeneca Pharmaceuticals • Bayer Corporation U.S. • Biofourmis • Boehringer Ingelheim Pharmaceuticals, Inc • Boston Scientific* • Merck and Co., Inc. • Novartis* • Pfizer • Relypsa • Sanofi-Aventis* • Xogenex	None	None	• American Regent • AstraZeneca* • Daiichi Sankyo • Genentech, Inc • Glaxo Smith Kline* • Merck and Co., Inc. • NIH† • Novartis* • PCORI† • Verily* • Eidos (DSMB)	• AHA†	• Defendant, patent dispute, 2019
Anastasia L. Armbruster	Content Reviewer—Joint Committee on Clinical Practice Guidelines	St. Louis College of Pharmacy	None	• AstraZeneca Pharmaceuticals	None	None	None	None
Andrew M. Kates	Content Reviewer—ACC/AHA	Washington University School of Medicine-Professor of Medicine Director, Cardiovascular Fellowship Program	None	None	None	None	None	None
Andrew Wang	Official Reviewer—AHA	Duke University Medical Center-Professor of Medicine	• American College of Physicians* • Cytokinetics • RioVant • UpToDate	None	None	• Myokardia*	• Abbott Vascular • AHA, <i>Circulation</i> Journal* • Medtronic • MyoKardia, Inc	• Defendant, Diagnosis of Infective Endocarditis, 2019
Anita Deswal	Content Reviewer—Joint Committee on Clinical Practice Guidelines	The University of Texas MD Anderson Cancer Center—Department Chair, Cardiology, Ting Tsung and Wei Fong Chao Distinguished Chair, Professor of Medicine	None	None	None	• NIH*	• ACC • AHA • Heart Failure Society of America†	None
Ann Bolger	Content Reviewer—ACC/AHA	University of California, San Francisco-Professor of Medicine	• General Electric	None	None	None	None	None

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Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Brian R. Lindman	Content Reviewer—ACC/AHA	Vanderbilt University Medical Center	None	None	None	• Edwards Lifesciences*	None	None
Bulent Gorenek	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Eskisehir Osmangazi University School of Medicine – Professor of Cardiology	• AstraZeneca • Sandoz	None	None	None	None	None
Carole A. Warnes	Content Reviewer—ACC/AHA	Mayo Clinic-Professor of Medicine	None	None	None	None	None	None
Cheryl Batzing	Content Reviewer—ACC/AHA Lay Reviewer	Church Ministries International—Donor Relations Manager	None	None	None	None	None	None
Christine C. Rekash	Content Reviewer—ACC/AHA Lay Reviewer	U.S. Department of Justice—Paralegal	• Heart Valve Voice	• Advocate Good Samaritan Hospital† • AHA • Bluhm Cardiovascular Institute at Northwestern Hospital†	None	None	• Edwards Life Sciences • Heart Valve Voice • PCORI	None
Daniel B. Mark	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Duke Clinical Research Institute—Professor of Medicine	None	None	None	• HeartFlow* • Merck and Co., Inc.*	• Merck and Co., Inc.*	None
Dave L. Dixon	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Virginia Commonwealth University School of Pharmacy	None	None	None	• Centers for Disease Control and Prevention* • Community Pharmacy Foundation*	• Accreditation Council for Clinical Lipidology† • American Pharmacists Association • American College of Pharmacy Cardiology Practice Research Network† • National Lipid Association†	None
David H. Adams	Content Reviewer—ACC/AHA	Mt. Sinai Medical Center	None	None	None	• Abbott • Medtronic • NeoChord	• Edwards Lifesciences* • Medtronic*	None
David E. Newby	Content Reviewer—ACC/AHA	University of Edinburgh Chancellor's Building—Professor of Cardiology	• AstraZeneca* • Bristol-Myers Squibb Company* • CellProthera • Eli-Lilly • Glaxo Smith Kline* • Jansen • Oncoarendi • Pfizer • Reckitt Benckiser Pharmaceuticals Inc. • Roche • Toshiba	None	None	• AstraZeneca* • Boehringer Ingelheim* • Bristol-Myers Squibb Company* • GlaxoSmithKline* • Merck and Co., Inc.* • Pfizer* • UCB Inc. (DSMB)	• AstraZeneca Pharmaceuticals • Bristol-Myers Squibb Company • CellProthera • Esperion • Infraredx	None
Jacqueline E. Tamis-Holland	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Mount Sinai Saint Luke's Hospital	None	None	None	• Internal-Minneapolis Heart Institute-North American Covid STEMI Registry†	• Abbott Vascular† • AHA† • Bronx Lebanon Hospital, Cardiology Fellowship Program Director† • Medscape/Heart.org • Merck and Co., Inc. • NIH† • The NGS Predict Study	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jeanne M. DeCara	Content Reviewer—ACC/AHA	University of Chicago Medicine	None	None	None	None	• Intersocietal Accreditation Commission†	None
José A. Joglar	Content Reviewer—Joint Committee on Clinical Practice Guidelines	UT Southwestern Medical Center—Professor, Internal Medicine. Program Director, Clinical Cardiac Electrophysiology Fellowship Program Professor	None	None	None	None	None	None
Joseph Edward Marine	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Johns Hopkins University School of Medicine	• ACC*	None	None	None	• UpToDate	None
Kim K. Birtcher	Content Reviewer—Joint Committee on Clinical Practice Guidelines	University of Washington—Director, Adult Congenital Heart Disease Program	• Jones & Bartlett Learning	None	None	None	None	None
Larry M. Baddour	Content Reviewer—ACC/AHA	Mayo Clinic, Rochester, MN	• Boston Scientific*	None	None	None	• UpToDate, Inc.*	None
Latha Palaniappan	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Stanford Medicine	• 23 and me • National Minority Cardiovascular Alliance	None	None	• NIH*	None	None
Lisa de las Fuentes	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Washington University, School of Medicine, Department of Medicine, Cardiovascular Division	• Acceleron • Altavant • Arena • Bayer Healthcare Pharmaceuticals • Express Scripts • Johnson & Johnson • Mentor Planning and Consulting • Phase Bio • V-wave • WebMD, LLC*	• Bayer Healthcare Pharmaceuticals* • Simply Speaking*	None	• Acceleron* • Altavant* • Bayer Healthcare Pharmaceuticals • Complexa* • Johnson & Johnson* • Liquidia* • Medtronic* • NIH* • Reata • Trio Analytics* • United Therapeutics* • University of Kentucky (DSMB) • University of Toronto†	• ACC† • AHA† • <i>Circulation Journals</i> , Editorial Board • Ironwood • Pulmonary Hypertension Association*	None
Mariann Piano	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Vanderbilt University	None	None	None	None	None	None
Mark Reisman	Content Reviewer—ACC/AHA	University of Washington Medical Center—Section Head, Interventional Cardiology	• Boston Scientific	None	None	None	None	None
Milind Y. Desai	Content Reviewer—ACC/AHA	Cleveland Clinic	None	None	None	None	None	None
Patrick Collier	Content Reviewer—AHA	Cleveland Clinic	None	None	None	None	None	None
Philippe Pibarot	Content Reviewer—ACC/AHA	Professor, Department of Medicine, Laval University Head of Cardiology Research, Institut Universitaire de Cardiologie et de Pneumologie de Québec / Québec Heart & Lung Institute	None	None	None	• Canadian Institutes of Health Research* • Cardiac Phoenix* • Edwards Lifesciences* • Medtronic* • V-Wave Ltd.*	None	None
Rebecca T. Hahn	Content Reviewer—ACC	Professor of Medicine at Columbia University Medical Center	• Edwards Lifesciences • Medtronic • Philips Healthcare	• Abbott Vascular • Baylis Medical • Siemens Healthineers	• NaviGate†	None	• Director of the Echo Core Lab†	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sandra Lauck	Content Reviewer—ACC/AHA	University of British Columbia, Vancouver, Canada	None	• Abbott • Edwards Lifesciences*	None	None	None	None
Suzanne Arnold	Content Reviewer—ACC/AHA	St. Luke's Mid America Heart Institute	None	None	None	None	• Abbott Laboratories	None
Terrence D. Welch	Content Reviewer—ACC/AHA	Dartmouth-Hitchcock Medical Center	None	None	None	None	None	None
Vinod H. Thourani	Content Reviewer—ACC	Piedmont Heart Institute	• Abbott Vascular • Boston Scientific • Edwards Lifesciences • Gore Medical • Jenavalve	None	None	None	• Abbott Medical • Medtronic†	None
Wendy Tsang	Content Reviewer—ACC/AHA	Toronto General Hospital	• UpToDate	None	None	• Heart and Stroke Foundation of Canada* • Peter Munk Cardiac Center Innovation Committee*	• Heart and Stroke Foundation of Canada*	None
William F. Armstrong	Content Reviewer—ACC/AHA	University of Michigan Professor of Medicine, Division of Cardiovascular Disease	None	None	None	None	None	• Defendant, medical malpractice, 2019
William Schuyler Jones	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Duke University Health System	• Bayer Healthcare Pharmaceuticals* • Janssen Pharmaceuticals, Inc*	None	None	• Bristol Myers Squibb • PCORI	None	None
Zachary D. Goldberger	Content Reviewer—Joint Committee on Clinical Practice Guidelines	University of Wisconsin School of Medicine and Public Health, Associate Professor of Medicine	None	None	None	None	None	None
Stephan Windecker	Content Reviewer—ACC/AHA	Inselspital Universitätsspital Bern—Direktor und Chefarzt, Universitätsklinik für Kardiologie	None	None	None	None	• Abbott* • Amgen* • Bayer* • Biotronik* • Boston Scientific* • Bristol-Myers Squibb • CSL Behring • Edwards Lifesciences* • Medtronic* • Polares Medical • SINO Medical Technologies, Inc	None

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