

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

# 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

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

## Writing Group Members\*

Rick A. Nishimura, MD, MACC, FAHA, *Co-Chair*  
Catherine M. Otto, MD, FACC, FAHA, *Co-Chair*

Robert O. Bonow, MD, MACC, FAHA†  
Blase A. Carabello, MD, FACC\*†  
John P. Erwin III, MD, FACC, FAHA†  
Lee A. Fleisher, MD, FACC, FAHA‡  
Hani Jneid, MD, FACC, FAHA, FSCAI§  
Michael J. Mack, MD, FACC\*||  
Christopher J. McLeod, MBChB, PhD, FACC, FAHA†  
Patrick T. O’Gara, MD, MACC, FAHA†

Vera H. Rigolin, MD, FACC¶  
Thoralf M. Sundt III, MD, FACC\*#  
Annemarie Thompson, MD\*\*

\*Focused Update writing group 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 Representative. ‡ACC/AHA Task Force on Clinical Practice Guidelines Liaison. §SCAI Representative. ||STS Representative. ¶ASE Representative. #AATS Representative. \*\*SCA Representative.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee on behalf of the Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee in January 2017, and the American Heart Association Executive Committee in February 2017.

The American College of Cardiology requests that this document be cited as follows: Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O’Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 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. *J Am Coll Cardiol* 2017;70:252-89.

This article has been copublished in *Circulation*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology ([www.acc.org](http://www.acc.org)) and the American Heart Association ([professional.heart.org](http://professional.heart.org)). For copies of this document, please contact the Elsevier Reprint Department via fax (212-633-3820) or e-mail ([reprints@elsevier.com](mailto:reprints@elsevier.com)).

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American College of Cardiology. Requests may be completed online via the Elsevier site (<http://www.elsevier.com/about/policies/author-agreement/obtaining-permission>).

**ACC/AHA Task Force Members**  
 Glenn N. Levine, MD, FACC, FAHA, *Chair*  
 Patrick T. O’Gara, MD, MACC, FAHA, *Chair-Elect*  
 Jonathan L. Halperin, MD, FACC, FAHA, *Immediate Past Chair*††

---

Sana M. Al-Khatib, MD, MHS, FACC, FAHA  
 Kim K. Birtcher, MS, PHARM.D, AACC  
 Biykem Bozkurt, MD, PhD, FACC, FAHA  
 Ralph G. Brindis, MD, MPH, MACC††  
 Joaquin E. Cigarroa, MD, FACC  
 Lesley H. Curtis, PhD, FAHA  
 Lee A. Fleisher, MD, FACC, FAHA

Federico Gentile, MD, FACC  
 Samuel Gidding, MD, FAHA  
 Mark A. Hlatky, MD, FACC  
 John Ikonomidis, MD, PhD, FAHA  
 José Joglar, MD, FACC, FAHA  
 Susan J. Pressler, PhD, RN, FAHA  
 Duminda N. Wijeyesundera, MD, PhD

††Former Task Force member; current member during the writing effort.

**TABLE OF CONTENTS**

<b>PREAMBLE</b> .....	254	<b>11.2. Antithrombotic Therapy for Prosthetic Valves</b> ..	267
<b>1. INTRODUCTION</b> .....	255	11.2.1. Diagnosis and Follow-Up .....	267
1.1. Methodology and Evidence Review .....	255	11.2.2. Medical Therapy: Recommendations .....	267
1.2. Organization of the Writing Group .....	255	<b>11.3. Bridging Therapy for Prosthetic Valves</b> .....	269
1.3. Document Review and Approval .....	256	11.3.1. Diagnosis and Follow-Up .....	269
<b>2. GENERAL PRINCIPLES</b> .....	257	11.3.2. Medical Therapy: Recommendations .....	269
2.4. Basic Principles of Medical Therapy .....	257	<b>11.6. Acute Mechanical Prosthetic Valve Thrombosis</b> ..	270
2.4.2. Infective Endocarditis Prophylaxis:		11.6.1. Diagnosis and Follow-Up:	
Recommendation .....	257	Recommendation .....	270
2.4.3. Anticoagulation for Atrial Fibrillation in		11.6.3. Intervention: Recommendation .....	271
Patients With VHD: Recommendations		<b>11.7. Prosthetic Valve Stenosis</b> .....	271
(New Section) .....	258	11.7.3. Intervention: Recommendation .....	272
<b>3. AORTIC STENOSIS</b> .....	259	<b>11.8. Prosthetic Valve Regurgitation</b> .....	273
3.2. Aortic Stenosis .....	259	11.8.3. Intervention: Recommendations .....	273
3.2.4. Choice of Intervention:		<b>12. INFECTIVE ENDOCARDITIS</b> .....	274
Recommendations .....	259	12.2. Infective Endocarditis .....	274
<b>7. MITRAL REGURGITATION</b> .....	261	12.2.3. Intervention: Recommendations .....	274
7.2. Stages of Chronic MR .....	261	<b>REFERENCES</b> .....	276
7.3. Chronic Primary MR .....	262	<b>APPENDIX 1</b>	
7.3.3. Intervention: Recommendations .....	262	Author Relationships With Industry and	
7.4. Chronic Secondary MR .....	264	Other Entities (Relevant) .....	283
7.4.3. Intervention: Recommendations .....	264	<b>APPENDIX 2</b>	
<b>11. PROSTHETIC VALVES</b> .....	265	Reviewer Relationships With Industry and	
11.1. Evaluation and Selection of Prosthetic Valves ..	265	Other Entities (Comprehensive) .....	284
11.1.2. Intervention: Recommendations .....	265	<b>APPENDIX 3</b>	
		Abbreviations .....	289

## PREAMBLE

---

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

### Intended Use

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 guidelines developed in collaboration with other organizations may have a global impact. Although guidelines may be used to inform regulatory or payer decisions, their intent is to improve patients' 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

Guideline recommended management is effective only when followed by healthcare providers and patients. Adherence to recommendations can be enhanced by shared decision making between healthcare providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

### Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) 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, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination of information at the point of care to healthcare professionals. Given time constraints of busy healthcare providers and the need to limit text, the current guideline format delineates that each recommendation be supported by limited text (ideally, <250 words) and hyperlinks to supportive evidence summary tables. Ongoing efforts to further limit text are underway.

Recognizing the importance of cost-value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of 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 are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new, potentially practice-changing study results that are relevant to an existing or new drug, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual (4) and other methodology articles (5-8).

### Selection of Writing Committee Members

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

### Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found [online](#). [Appendix 1](#) of the current document lists writing committee members' relevant RWI. For the purposes of full transparency, writing committee members' comprehensive disclosure information is available [online](#), as is comprehensive [disclosure information](#) for the Task Force.

### Evidence Review and Evidence Review Committees

When developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (4-7). 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 (ERC) is commissioned when there are 1 or more questions deemed of utmost clinical importance that merit formal

systematic review. This systematic review will strive to determine which patients are most likely to benefit from a drug, device, or treatment strategy and to what degree. Criteria for commissioning an ERC and formal systematic review include: a) the absence of a current authoritative systematic review, b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, c) the relevance to a substantial number of patients, and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. When a formal systematic review has been commissioned, the recommendations developed by the writing committee on the basis of the systematic review are marked with “SR”.

### Guideline-Directed Management and Therapy

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

### Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1) (4-6).

Glenn N. Levine, MD, FACC, FAHA  
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

## 1. INTRODUCTION

The focus of the “2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease” (9,10) (2014 VHD guideline) was the diagnosis and management of adult patients with valvular heart disease (VHD). The field of VHD is rapidly progressing, with new knowledge of the natural history of patients with valve disease, advances in diagnostic imaging, and improvements in catheter-based and surgical interventions. Several randomized controlled trials (RCTs) have been published since the 2014 VHD guideline, particularly with regard to the outcomes of interventions. Major areas

of change include indications for transcatheter aortic valve replacement (TAVR), surgical management of the patient with primary and secondary mitral regurgitation (MR), and management of patients with valve prostheses.

All recommendations (new, modified, and unchanged) for each clinical section are included to provide a comprehensive assessment. The text explains new and modified recommendations, whereas recommendations from the previous guideline that have been deleted or superseded no longer appear. Please consult the full-text version of the 2014 VHD guideline (10) for text and evidence tables supporting the unchanged recommendations and for clinical areas not addressed in this focused update. Individual recommendations in this focused update will be incorporated into the full-text guideline in the future. Recommendations from the prior guideline that remain current have been included for completeness but the LOE reflects the COR/LOE system used when initially developed. New and modified recommendations in this focused update reflect the latest COR/LOE system, in which LOE B and C are subcategorized for greater specificity (4-7). The section numbers correspond to the full-text guideline sections.

### 1.1. Methodology and Evidence Review

To identify key data that might influence guideline recommendations, the Task Force and members of the 2014 VHD guideline writing committee reviewed clinical trials that were presented at the annual scientific meetings of the ACC, AHA, European Society of Cardiology, and other groups and that were published in peer-reviewed format from October 2013 through November 2016. The evidence is summarized in tables in the [Online Data Supplement](#).

### 1.2. Organization of the Writing Group

For this focused update, representative members of the 2014 VHD writing committee were invited to participate, and they were joined by additional invited members to form a new writing group, referred to as the 2017 focused update writing group. Members were required to disclose all RWI relevant to the data under consideration. The group was composed of experts representing cardiovascular medicine, cardiovascular imaging, interventional cardiology, electrophysiology, cardiac surgery, and cardiac anesthesiology. The writing group included representatives from the ACC, AHA, American Association for Thoracic Surgery (AATS), American Society of Echocardiography (ASE), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Anesthesiologists (SCA), and Society of Thoracic Surgeons (STS).

**TABLE 1** Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS I (STRONG)</b> <span style="float: right;">Benefit &gt;&gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is recommended</li> <li>■ Is indicated/useful/effective/beneficial</li> <li>■ Should be performed/administered/other</li> <li>■ Comparative-Effectiveness Phrases†:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>○ Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>■ High-quality evidence‡ from more than 1 RCT</li> <li>■ Meta-analyses of high-quality RCTs</li> <li>■ One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS IIa (MODERATE)</b> <span style="float: right;">Benefit &gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is reasonable</li> <li>■ Can be useful/effective/beneficial</li> <li>■ Comparative-Effectiveness Phrases†:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>○ It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more RCTs</li> <li>■ Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS IIb (WEAK)</b> <span style="float: right;">Benefit ≥ Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ May/might be reasonable</li> <li>■ May/might be considered</li> <li>■ Usefulness/effectiveness is unknown/unclear/uncertain or not well established</li> </ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>■ Meta-analyses of such studies</li> </ul>
<b>CLASS III: No Benefit (MODERATE)</b> <span style="float: right;">Benefit = Risk</span> <i>(Generally, LOE A or B use only)</i> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is not recommended</li> <li>■ Is not indicated/useful/effective/beneficial</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"> <li>■ Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>■ Meta-analyses of such studies</li> <li>■ Physiological or mechanistic studies in human subjects</li> </ul>
<b>CLASS III: Harm (STRONG)</b> <span style="float: right;">Risk &gt; Benefit</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Potentially harmful</li> <li>■ Causes harm</li> <li>■ Associated with excess morbidity/mortality</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO (Expert Opinion)</b> 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 I and IIa; 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.

### 1.3. Document Review and Approval

The focused update was reviewed by 2 official reviewers each nominated by the ACC and AHA; 1 reviewer each from the AATS, ASE, SCAI, SCA, and STS; and 40 content reviewers. Reviewers' RWI information is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the AATS, ASE, SCAI, SCA, and STS.

## 2. GENERAL PRINCIPLES

### 2.4. Basic Principles of Medical Therapy

#### 2.4.2. Infective Endocarditis Prophylaxis: Recommendation

With the absence of RCTs that demonstrated the efficacy of antibiotic prophylaxis to prevent infective endocarditis (IE), the practice of antibiotic prophylaxis has been questioned by national and international medical societies (11-14). Moreover, there is not universal agreement on which patient populations are at higher risk of developing IE than the general population. Protection from endocarditis in patients undergoing high-risk procedures is not guaranteed. A prospective study demonstrated that prophylaxis given to patients for what is typically considered a high-risk dental procedure reduced but did not eliminate the incidence of bacteremia (15). A 2013 Cochrane Database systematic review of antibiotic prophylaxis 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 longstanding clinical dilemma (13). Epidemiological data conflict with regard to incidence of IE after adoption of more limited prophylaxis, as recommended by the AHA and European Society of Cardiology (16-20), and no prophylaxis, as recommended by the U.K. NICE (National Institute for Health and Clinical Excellence) guidelines (21). Some studies indicate no increase in incidence of endocarditis with limited or no prophylaxis, whereas others suggest that IE cases have increased with adoption of the new guidelines (16-22). The consensus of the writing group is that antibiotic prophylaxis is reasonable for the subset of patients at increased 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, absent known active infection.

### Recommendation for IE Prophylaxis

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
Ila	C-LD	<p>Prophylaxis against IE 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 the following (13,15,23-29):</p> <ol style="list-style-type: none"> <li>1. Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts.</li> <li>2. Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords.</li> <li>3. Previous IE.</li> <li>4. 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.</li> <li>5. Cardiac transplant with valve regurgitation due to a structurally abnormal valve.</li> </ol>	<p><b>MODIFIED:</b> LOE updated from B to C-LD. Patients with transcatheter prosthetic valves and patients with prosthetic material used for valve repair, such as annuloplasty rings and chords, were specifically identified as those to whom it is reasonable to give IE prophylaxis. This addition is based on observational studies demonstrating the increased risk of developing IE and high risk of adverse outcomes from IE in these subgroups. Categories were rearranged for clarity to the caregiver.</p>

See Online Data Supplements 1 and 2.

The risk of developing IE is higher in patients with underlying VHD. However, even in patients at high risk of IE, evidence for the efficacy of antibiotic prophylaxis is lacking. The lack of supporting evidence, along with the risk of anaphylaxis and increasing bacterial resistance to antimicrobials, led to a revision in the 2007 AHA recommendations for prophylaxis limited to those patients at highest risk of adverse outcomes with IE (11). These included patients with a history of prosthetic valve replacement, patients with prior IE, select patients with congenital heart disease, and cardiac transplant recipients. IE has been reported to occur after TAVR at rates equal to or exceeding those associated with surgical aortic valve replacement (AVR) and is associated with a high 1-year mortality rate of 75% (30,31). IE may also occur after valve repair in which prosthetic material is used, usually necessitating urgent operation, which has high in-hospital and 1-year mortality rates (32,33). IE appears to be more common in heart transplant recipients than in the general population, according to limited data (23). 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 (23). Persons at risk of developing bacterial IE should establish and maintain the best possible oral health to reduce potential sources of bacterial seeding. Optimal oral health is maintained through regular professional dental care and the use of appropriate dental products, such as manual, powered, and ultrasonic toothbrushes; dental floss; and other plaque-removal devices.

2.4.3. Anticoagulation for Atrial Fibrillation in Patients With VHD:  
Recommendations (New Section)

Recommendations for Anticoagulation for Atrial Fibrillation (AF) in Patients With VHD

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B-NR	Anticoagulation with a vitamin K antagonist (VKA) is indicated for patients with rheumatic mitral stenosis (MS) and AF (34,35).	<b>MODIFIED:</b> VKA as opposed to the direct oral anticoagulants (DOACs) are indicated in patients with AF and rheumatic MS to prevent thromboembolic events. The RCTs of DOACs versus VKA have not included patients with MS. The specific recommendation for anticoagulation of patients with MS is contained in a subsection of the topic on anticoagulation (previously in Section 6.2.2).
See Online Data Supplements 3 and 4.			
<p>A retrospective analysis of administrative claims databases (&gt;20,000 DOAC-treated patients) showed no difference in the incidence of stroke or major bleeding in patients with rheumatic and nonrheumatic MS if treated with DOAC versus warfarin (35). However, the writing group continues to recommend the use of VKA for patients with rheumatic MS until further evidence emerges on the efficacy of DOAC in this population. (See Section 6.2.2 on Medical Management of Mitral Stenosis in the 2014 guideline.)</p>			
I	C-LD	Anticoagulation is indicated in patients with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or greater with native aortic valve disease, tricuspid valve disease, or MR (36-38).	<b>NEW:</b> Post hoc subgroup analyses of large RCTs comparing DOAC versus warfarin in patients with AF have analyzed patients with native valve disease other than MS and patients who have undergone cardiac surgery. These analyses consistently demonstrated that the risk of stroke is similar to or higher than that of patients without VHD. Thus, the indication for anticoagulation in these patients should follow GDMT according to the CHA <sub>2</sub> DS <sub>2</sub> -VASc score (35-38).
See Online Data Supplements 3 and 4.			
<p>Many patients with VHD have AF, yet these patients were not included in the original studies evaluating the risk of stroke or in the development of the risk schema such as CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc (39,40). Post hoc subgroup analyses of large RCTs comparing apixaban, rivaroxaban, and dabigatran (DOACs) versus warfarin (36-38) included patients with VHD, and some included those with bioprosthetic valves or those undergoing valvuloplasty. Although the criteria for nonvalvular AF differed for each trial, patients with significant MS and valve disease requiring an intervention were excluded. There is no clear evidence that the presence of native VHD other than rheumatic MS need be considered in the decision to anticoagulate a patient with AF. On the basis of these findings, the writing group supports the use of anticoagulation in patients with VHD and AF when their CHA<sub>2</sub>DS<sub>2</sub>-VASc score is 2 or greater. Patients with a bioprosthetic valve or mitral repair and AF are at higher risk for embolic events and should undergo anticoagulation irrespective of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.</p>			
Ia	C-LD	It is reasonable to use a DOAC as an alternative to a VKA in patients with AF and native aortic valve disease, tricuspid valve disease, or MR and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or greater (35-38).	<b>NEW:</b> Several thousand patients with native VHD (exclusive of more than mild rheumatic MS) have been evaluated in RCTs comparing DOACs versus warfarin. Subgroup analyses have demonstrated that DOACs, when compared with warfarin, appear as effective and safe in patients with VHD as in those without VHD.
See Online Data Supplements 3 and 4.			

DOACs appear to be as effective and safe in patients with VHD as they are in those without VHD. In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trials, 2,003, 4,808, and 3,950 patients, respectively, had significant VHD (36-38). This included MR, mild MS, aortic regurgitation, aortic stenosis (AS), and tricuspid regurgitation. These trials consistently demonstrated at least equivalence to warfarin in reducing stroke and systemic embolism. Retrospective analyses of administrative claims databases (>20,000 DOAC-treated patients) correlate with these findings (35). In addition, the rate of intracranial hemorrhage in each trial was lower among patients randomized to dabigatran, rivaroxaban, or apixaban than among those randomized to warfarin, regardless of the presence of VHD (36-38). There is an increased risk of bleeding in patients with VHD versus those without VHD, irrespective of the choice of the anticoagulant.

### 3. AORTIC STENOSIS

#### 3.2. Aortic Stenosis

##### 3.2.4. Choice of Intervention: Recommendations

The recommendations for choice of intervention for AS apply to both surgical AVR and TAVR; indications for AVR are discussed in Section 3.2.3 in the 2014 VHD guideline. The integrative approach to assessing risk of surgical AVR or TAVR is discussed in Section 2.5 in the 2014 VHD

guideline. The choice of proceeding with surgical AVR versus TAVR is based on multiple factors, including the surgical risk, patient frailty, comorbid conditions, and patient preferences and values (41). Concomitant severe coronary artery disease may also affect the optimal intervention because severe multivessel coronary disease may best be served by surgical AVR and coronary artery bypass graft surgery (CABG). See **Figure 1** for an algorithm on choice of TAVR versus surgical AVR.

#### Recommendations for Choice of Intervention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	C	For patients in whom TAVR or high-risk surgical AVR is being considered, a heart valve team consisting of an integrated, multidisciplinary group of healthcare professionals with expertise in VHD, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery should collaborate to provide optimal patient care.	2014 recommendation remains current.
I	B-NR	Surgical AR is recommended for symptomatic patients with severe AS (Stage D) and asymptomatic patients with severe AS (Stage C) who meet an indication for AVR when surgical risk is low or intermediate (42,43).	<b>MODIFIED:</b> LOE updated from A to B-NR. Prior recommendations for intervention choice did not specify patient symptoms. The patient population recommended for surgical AVR encompasses both symptomatic and asymptomatic patients who meet an indication for AVR with low-to-intermediate surgical risk. This is opposed to the patient population recommended for TAVR, in whom symptoms are required to be present. Thus, all recommendations for type of intervention now specify the symptomatic status of the patient.
<p>AVR is indicated for survival benefit, improvement in symptoms, and improvement in left ventricular (LV) systolic function in patients with severe symptomatic AS (Section 3.2.3 in the 2014 VHD guideline) (42-48). Given the magnitude of the difference in outcomes between those undergoing AVR and those who refuse AVR in historical series, an RCT of AVR versus medical therapy would not be appropriate in patients with a low-to-intermediate surgical risk (Section 2.5 in the 2014 VHD guideline). Outcomes after surgical AVR are excellent in patients who do not have a high procedural risk (43-46,48). 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 (43-46,48). The choice of prosthetic valve type is discussed in Section 11.1 of this focused update.</p>			
I	A	Surgical AVR or TAVR is recommended for symptomatic patients with severe AS (Stage D) and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences (49-51).	<b>MODIFIED:</b> COR updated from IIa to I, LOE updated from B to A. Longer-term follow-up and additional RCTs have demonstrated that TAVR is equivalent to surgical AVR for severe symptomatic AS when surgical risk is high.
<p>TAVR has been studied in RCTs, as well as in numerous observational studies and multicenter registries that include large numbers of high-risk patients with severe symptomatic AS (49,50,52-56). In the PARTNER (Placement of Aortic Transcatheter Valve) IA trial of a balloon-expandable valve (50,53), TAVR (n=348) was noninferior to surgical AVR (n=351) for all-cause death at 30 days, 1 year, 2 years, and 5 years (p=0.001) (53,54). The risk of death at 5 years was 67.8% in the TAVR group, compared with 62.4% in the surgical AVR group (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 0.86 to 1.24; p=0.76) (50). TAVR was performed by the transfemoral approach in 244 patients and the transapical approach in 104 patients. There was no structural valve deterioration requiring repeat AVR in either the TAVR or surgical AVR groups.</p> <p>In a prospective study that randomized 795 patients to either self-expanding TAVR or surgical AVR, TAVR was associated with an intention-to-treat 1-year survival rate of 14.2%, versus 19.1% with surgical AVR, equivalent to an absolute risk reduction of 4.9% (49). The rate of death or stroke at 3 years was lower with TAVR than with surgical AVR (37.3% versus 46.7%; p=0.006) (51). The patient's values and preferences, comorbidities, vascular access, anticipated functional outcome, and length of survival after AVR should be considered in the selection of surgical AVR or TAVR for those at high surgical risk. The specific choice of a balloon-expandable valve or self-expanding valve depends on patient anatomy and other considerations (57). TAVR has not been evaluated for asymptomatic patients with severe AS who have a high surgical risk. In these patients, frequent clinical monitoring for symptom onset is appropriate, as discussed in Section 2.3.3 in the 2014 VHD guideline.</p>			

See Online Data Supplements 5 and 9 (Updated From 2014 VHD Guideline)

See Online Data Supplement 9 (Updated From 2014 VHD Guideline)



(continued)



See Online Data Supplements 5 and 9  
(Updated From 2014 VHD  
Guideline)

**TAVR is recommended for symptomatic patients with severe AS (Stage D) and a prohibitive risk for surgical AVR who have a predicted post-TAVR survival greater than 12 months (58-61).**

**MODIFIED:** LOE updated from B to A. Longer-term follow-up from RCTs and additional observational studies has demonstrated the benefit of TAVR in patients with a prohibitive surgical risk.

TAVR was compared with standard therapy in a prospective RCT of patients with severe symptomatic AS who were deemed inoperable (53,58,60). The rate of all-cause death at 2 years was lower with TAVR (43.3%) (HR: 0.58; 95% CI: 0.36 to 0.92; p=0.02) than with standard medical therapy (68%) (53,58,60). Standard therapy included percutaneous aortic balloon dilation in 84%. There was a reduction in repeat hospitalization with TAVR (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 TAVR, compared with 58% of patients receiving standard therapy (p<0.001). However, the rate of major stroke was higher with TAVR 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 TAVR versus 1.1% with standard therapy (p<0.001) (53,58,60).

Similarly, in a nonrandomized study of 489 patients with severe symptomatic AS and extreme surgical risk treated with a self-expanding TAVR valve, the rate of all-cause death at 12 months was 26% with TAVR, compared with an expected mortality rate of 43% if patients had been treated medically (59).

Thus, in patients with severe symptomatic AS who are unable to undergo surgical AVR because of a prohibitive surgical risk and who have an expected survival of >1 year after intervention, TAVR is recommended to improve survival and reduce symptoms. This decision should be made only after discussion with the patient about the expected benefits and possible complications of TAVR. Patients with severe AS are considered to have a prohibitive surgical risk if they have a predicted risk with surgery of death or major morbidity (all causes) >50% at 30 days; disease affecting ≥3 major organ systems that is not likely to improve postoperatively; or anatomic factors that preclude or increase the risk of cardiac surgery, such as a heavily calcified (e.g., porcelain) aorta, prior radiation, or an arterial bypass graft adherent to the chest wall (58-61).



See Online Data Supplements 5 and 9  
(Updated From 2014 VHD  
Guideline)

**TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS (Stage D) and an intermediate surgical risk, depending on patient-specific procedural risks, values, and preferences (62-65).**

**NEW:** New RCT showed noninferiority of TAVR to surgical AVR in symptomatic patients with severe AS at intermediate surgical risk.

In the PARTNER II (Placement of Aortic Transcatheter Valve II) RCT (62), which enrolled symptomatic patients with severe AS at intermediate risk (STS score ≥4%), there was no difference between TAVR and surgical AVR for the primary endpoint of all-cause death or disabling stroke at 2 years (HR: 0.89; 95% CI: 0.73 to 1.09; p=0.25). All-cause death occurred in 16.7% of those randomized to TAVR, compared with 18.0% of those treated with surgical AVR. Disabling stroke occurred in 6.2% of patients treated with TAVR and 6.3% of patients treated with surgical AVR (62).

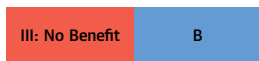
In an observational study of the SAPIEN 3 valve (63), TAVR was performed in 1,077 intermediate-risk patients with severe symptomatic AS, with the transfemoral approach used in 88% of patients. At 1 year, the rate of all-cause death was 7.4%, disabling stroke occurred in 2%, reintervention was required in 1%, and moderate or severe paravalvular aortic regurgitation was seen in 2%. In a propensity score-matched comparison of SAPIEN 3 TAVR patients and PARTNER 2A surgical AVR patients, TAVR was both noninferior and superior to surgical AVR (propensity score pooled weighted proportion difference: -9.2%; 95% CI: -13.0 to -5.4; p<0.0001) (63,66).

When the choice of surgical AVR or TAVR is being made in an individual patient at intermediate surgical risk, 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 surgical AVR (Section 11 of this focused update) versus a TAVR is an important consideration and is influenced by durability considerations, because durability of transcatheter valves beyond 3 and 4 years is not yet known (65). TAVR has not been studied in patients with severe asymptomatic AS who have an intermediate or low surgical risk. In these patients, frequent clinical monitoring for symptom onset is appropriate, as discussed in Section 2.3.3 in the 2014 VHD guideline. The specific choice of a balloon-expandable valve or self-expanding valve depends on patient anatomy and other considerations (41,57).



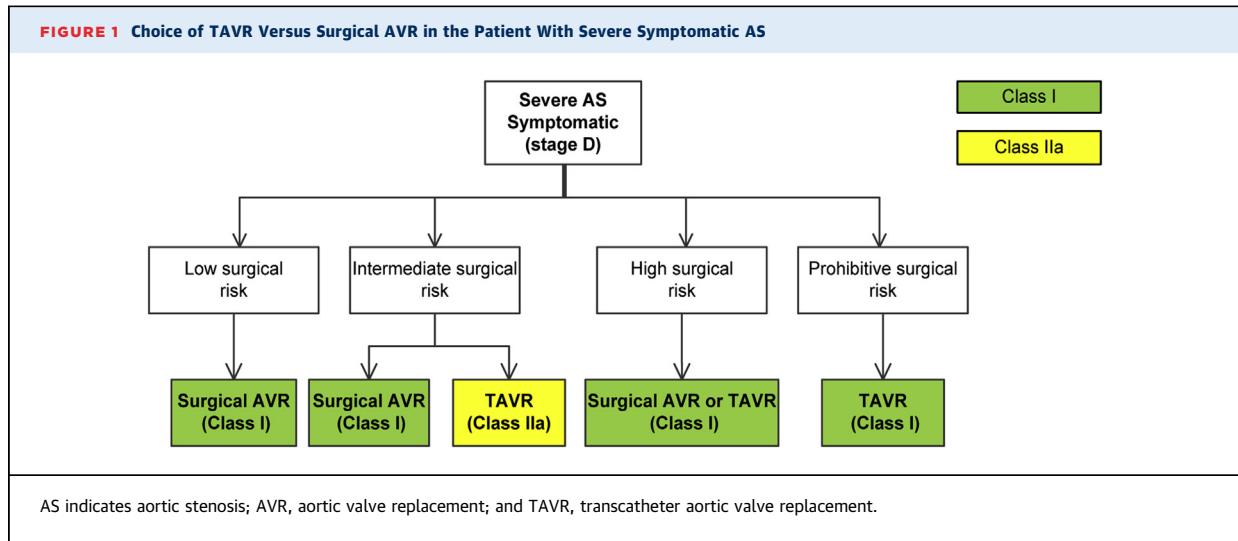
**Percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or TAVR for symptomatic patients with severe AS.**

2014 recommendation remains current.



**TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (61).**

2014 recommendation remains current.



## 7. MITRAL REGURGITATION

### 7.2. Stages of Chronic MR

In chronic *secondary* MR, the mitral valve leaflets and chords usually are normal (Table 2 in this focused update;

Table 16 from the 2014 VHD guideline). Instead, MR is associated with severe LV dysfunction due to coronary artery disease (ischemic chronic secondary MR) or idiopathic myocardial disease (nonischemic chronic secondary MR). The abnormal and dilated left ventricle causes

**TABLE 2 Stages of Secondary MR (Table 16 in the 2014 VHD Guideline)**

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	<ul style="list-style-type: none"> <li>Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>No MR jet or small central jet area &lt;20% LA on Doppler</li> <li>Small vena contracta &lt;0.30 cm</li> </ul>	<ul style="list-style-type: none"> <li>Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities</li> <li>Primary myocardial disease with LV dilation and systolic dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
B	Progressive MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with mild tethering of mitral leaflet</li> <li>Annular dilation with mild loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO &lt;0.40 cm<sup>2</sup>†</li> <li>Regurgitant volume &lt;60 mL</li> <li>Regurgitant fraction &lt;50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
C	Asymptomatic severe MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</li> <li>Annular dilation with severe loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO ≥0.40 cm<sup>2</sup>†</li> <li>Regurgitant volume ≥60 mL</li> <li>Regurgitant fraction ≥50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
D	Symptomatic severe MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</li> <li>Annular dilation with severe loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO ≥0.40 cm<sup>2</sup>†</li> <li>Regurgitant volume ≥60 mL</li> <li>Regurgitant fraction ≥50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>HF symptoms due to MR persist even after revascularization and optimization of medical therapy</li> <li>Decreased exercise tolerance</li> <li>Exertional dyspnea</li> </ul>

\*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.

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

papillary muscle displacement, which in turn results in leaflet tethering with associated annular dilation that prevents adequate leaflet coaptation. 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 1 component of the disease, with clinical outcomes also related to severe LV systolic dysfunction, coronary disease, idiopathic myocardial disease, or other diseases affecting the heart muscle. Thus, restoration of mitral valve competence is not curative. The optimal criteria for defining severe secondary MR have been controversial. In patients with secondary MR, some data suggest that, compared with primary MR, adverse outcomes are associated with a smaller calculated effective regurgitant orifice, possibly because of the fact that a smaller regurgitant volume may still represent a large regurgitant fraction in the presence of compromised LV systolic function (and low total stroke volume) added to the effects of elevated filling pressures. In addition, severity of secondary MR

may increase over time because of the associated progressive LV systolic dysfunction and dysfunction due to adverse remodeling of the left ventricle. Finally, Doppler methods for calculations of effective regurgitant orifice area by the flow convergence method may underestimate severity because of the crescentic shape of the regurgitant orifice, and multiple parameters must be used to determine the severity of MR (67,68). Even so, on the basis of the criteria used for determination of “severe” MR in RCTs of surgical intervention for secondary MR (69-72), the recommended definition of severe secondary MR is now the same as for primary MR (effective regurgitant orifice  $\geq 0.4$  cm<sup>2</sup> and regurgitant volume  $\geq 60$  mL), with the understanding that effective regurgitant orifice cutoff of  $>0.2$  cm<sup>2</sup> is more sensitive and  $>0.4$  cm<sup>2</sup> is more specific for severe MR. However, it is important to integrate the clinical and echocardiographic findings together to prevent unnecessary operation when the MR may not be as severe as documented on noninvasive studies.

### 7.3. Chronic Primary MR

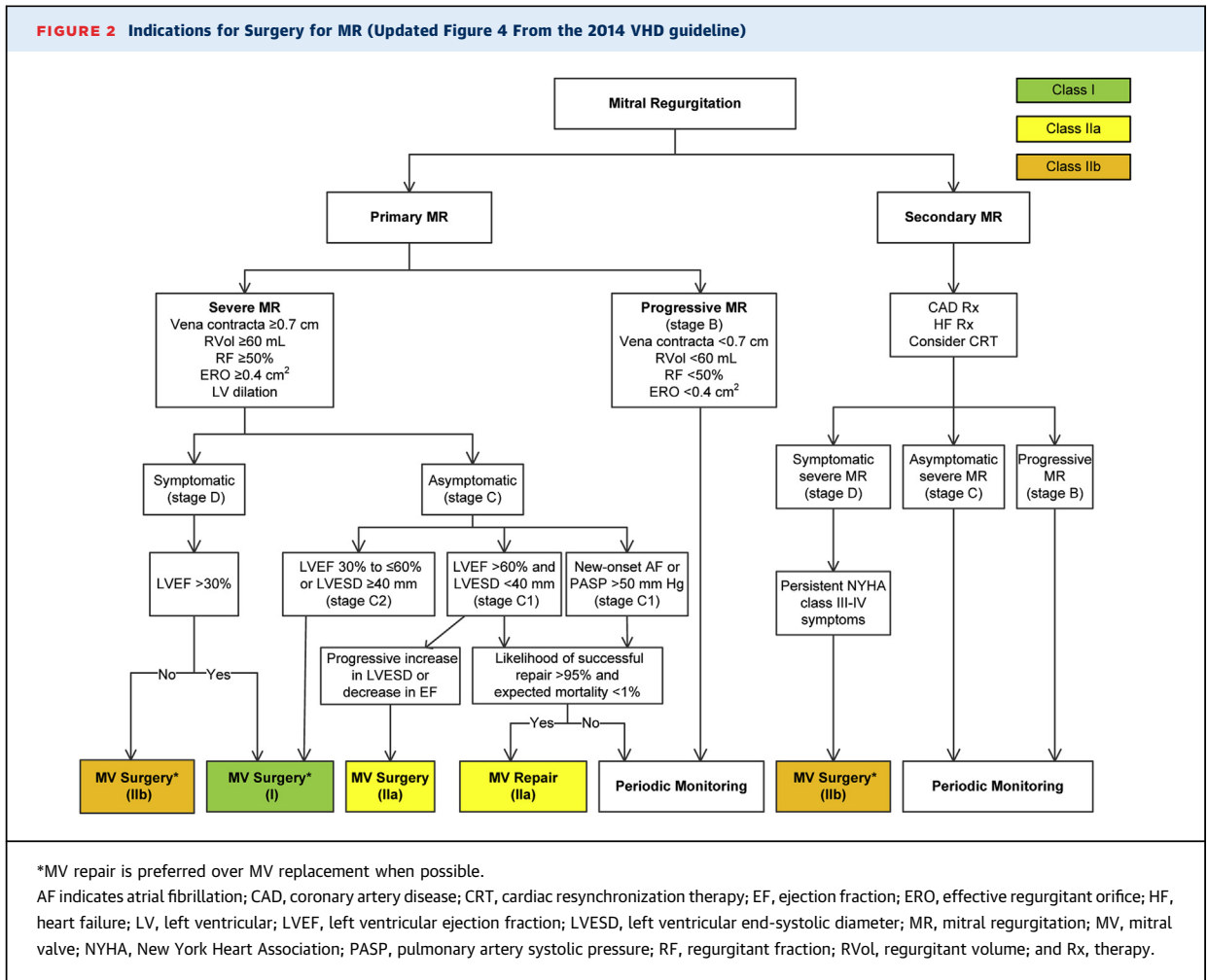
#### 7.3.3. Intervention: Recommendations

#### Recommendations for Chronic Primary MR Intervention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B	Mitral valve surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF greater than 30% (73-75).	2014 recommendation remains current.
I	B	Mitral valve surgery is recommended for asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30% to 60% and/or left ventricular end-systolic diameter [LVESD] $\geq 40$ mm, stage C2) (76-82).	2014 recommendation remains current.
I	B	Mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet (83-99).	2014 recommendation remains current.
I	B	Mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished (84,89,95,100-104).	2014 recommendation remains current.
I	B	Concomitant mitral valve repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications (105).	2014 recommendation remains current.

(continued)

IIa	B	<p>Mitral valve repair is reasonable in asymptomatic patients with chronic severe primary MR (stage C1) with preserved LV function (LVEF &gt;60% and LVESD &lt;40 mm) in whom the likelihood of a successful and durable repair without residual MR is greater than 95% with an expected mortality rate of less than 1% when performed at a Heart Valve Center of Excellence (101,106-112).</p>	<p>2014 recommendation remains current.</p>
IIa	C-LD	<p>Mitral valve surgery is reasonable for asymptomatic patients with chronic severe primary MR (stage C1) and preserved LV function (LVEF &gt;60% and LVESD &lt;40 mm) with a progressive increase in LV size or decrease in ejection fraction (EF) on serial imaging studies (112-115). (Figure 2)</p>	<p><b>NEW:</b> Patients with severe MR who reach an EF ≤60% or LVESD ≥40 have already developed LV systolic dysfunction, so operating before reaching these parameters, particularly with a progressive increase in LV size or decrease in EF on serial studies, is reasonable.</p>
<p>See Online Data Supplement 17 (Updated From 2014 VHD Guideline)</p>			
<p>There is concern that the presence of MR leads to progressively more severe MR ("mitral regurgitation begets mitral regurgitation"). The concept is that the initial level of MR causes LV dilatation, which increases stress on the mitral apparatus, causing further damage to the valve apparatus, more severe MR and further LV dilatation, 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 EF ≤60% or LVESD ≥40 have already developed LV systolic dysfunction (112-115). One study has suggested that for LV function and size to return to normal after mitral valve repair, the left ventricular ejection fraction (LVEF) should be &gt;64% and LVESD &lt;37 mm (112). Thus, when longitudinal follow-up demonstrates a progressive decrease of EF toward 60% or a progressive increase in LVESD approaching 40 mm, it is reasonable to consider intervention. Nonetheless, the asymptomatic patient with stable LV dimensions and excellent exercise capacity can be safely observed (116).</p>			
IIa	B	<p>Mitral valve repair is reasonable for asymptomatic patients with chronic severe nonrheumatic primary MR (stage C1) and preserved LV function (LVEF &gt;60% and LVESD &lt;40 mm) in whom there is a high likelihood of a successful and durable repair with 1) new onset of AF or 2) resting pulmonary hypertension (pulmonary artery systolic arterial pressure &gt;50 mm Hg) (111,117-123).</p>	<p>2014 recommendation remains current.</p>
IIa	C	<p>Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B) when undergoing cardiac surgery for other indications.</p>	<p>2014 recommendation remains current.</p>
IIb	C	<p>Mitral valve surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF less than or equal to 30% (stage D).</p>	<p>2014 recommendation remains current.</p>
IIb	B	<p>Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for heart failure (HF) (124).</p>	<p>2014 recommendation remains current.</p>
III: Harm	B	<p>MVR should not be performed for the treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless mitral valve repair has been attempted and was unsuccessful (84,89,90,95).</p>	<p>2014 recommendation remains current.</p>



## 7.4. Chronic Secondary MR

### 7.4.3. Intervention: Recommendations

Chronic severe secondary MR adds volume overload to a decompensated LV and worsens prognosis. However, there are only sparse data to indicate that correcting MR prolongs life or even improves symptoms over an extended time.

Percutaneous mitral valve repair provides a less invasive alternative to surgery but is not approved for clinical use for this indication in the United States (70,72,125-127). The results of RCTs examining the efficacy of percutaneous mitral valve repair in patients with secondary MR are needed to provide information on this patient group (128,129).

## Recommendations for Secondary MR Intervention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
IIa	C	Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.	2014 recommendation remains current.
IIa	B-R	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA class III to IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT for HF (69,70,125,127,130-139).	<b>NEW:</b> An RCT has shown that mitral valve repair is associated with a higher rate of recurrence of moderate or severe MR than that associated with mitral valve replacement (MVR) in patients with severe, symptomatic, ischemic MR, without a difference in mortality rate at 2 years' follow-up.

(continued)

In an RCT of mitral valve repair versus MVR in 251 patients with severe ischemic MR, mortality rate at 2 years was 19.0% in the repair group and 23.2% in the replacement group (p=0.39) (70). There was no difference between repair and MVR in LV remodeling. The rate of recurrence of moderate or severe MR over 2 years was higher in the repair group than in the replacement group (58.8% versus 3.8%, p<0.001), leading to a higher incidence of HF and repeat hospitalizations in the repair group (70). The high mortality rate at 2 years in both groups emphasizes the poor prognosis of secondary MR. The lack of apparent benefit of valve repair over valve replacement in secondary MR versus primary MR highlights that primary and secondary MR are 2 different diseases (69,125,127,130-139).

IIb	B	Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF (125,127,130-140).	2014 recommendation remains current.
-----	---	--	--------------------------------------

IIb	B-R	In patients with chronic, moderate, ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain (71,72).	<b>MODIFIED:</b> LOE updated from C to B-R. The 2014 recommendation supported mitral valve repair in this group of patients. An RCT showed no clinical benefit of mitral repair in this population of patients, with increased risk of postoperative complications.
-----	-----	--	---

See Online Data Supplement 18 (Updated From 2014 VHD Guideline)

In an RCT of 301 patients with moderate ischemic MR undergoing CABG, mortality rate at 2 years was 10.6% in the group undergoing CABG alone and 10.0% in the group undergoing CABG plus mitral valve repair (HR in the combined-procedure group = 0.90; 95% CI: 0.45 to 1.83; p=0.78) (71). There was a higher rate of moderate or severe residual MR in the CABG-alone group (32.3% versus 11.2%; p<0.001), even though LV reverse remodeling was similar in both groups (71). Although rates of hospital readmission and overall serious adverse events were similar in the 2 groups, neurological events and supraventricular arrhythmias were more frequent with combined CABG and mitral valve repair. Thus, only weak evidence to support mitral repair for moderate secondary MR at the time of other cardiac surgery is currently available (71,72).

## 11. PROSTHETIC VALVES

### 11.1. Evaluation and Selection of Prosthetic Valves

#### 11.1.2. Intervention: Recommendations

#### Recommendations for Intervention of Prosthetic Valves

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	C-LD	The choice of type of prosthetic heart valve should be 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 risk associated with reintervention (141-146).	<b>MODIFIED:</b> LOE updated from C to C-LD. In choosing the type of prosthetic valve, the potential need for and risk of "reoperation" was updated to risk associated with "reintervention." The use of a transcatheter valve-in-valve procedure may be considered for decision making on the type of valve, but long-term follow-up is not yet available, and some bioprosthetic valves, particularly the smaller-sized valves, will not be suitable for a valve-in-valve replacement. Multiple other factors to be considered in the choice of type of valve for an individual patient; these factors are outlined in the text. More emphasis has been placed on shared decision making between the caregiver and patient.

See Online Data Supplement 20 (Updated From 2014 VHD Guideline)

The choice of valve prosthesis in an individual patient is based on consideration of several factors, including valve durability, expected hemodynamics for a specific valve type and size, surgical or interventional risk, the potential need for long-term anticoagulation, and patient values and preferences (147-149). Specifically, the trade-off between the potential need for reintervention for bioprosthetic structural valve deterioration and the risk associated with long-term anticoagulation should be discussed in detail with the patient (142-145). 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 VKA

(continued)

therapy because of the inconvenience of monitoring, the attendant dietary and medication interactions, and the need to restrict participation in some types of athletic activity. Several other factors must be taken into consideration in a decision about the type of valve prosthesis, including other comorbidities (Table 3). Age is important because 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 (142,143,150,151). A mechanical valve might be a prudent choice for patients for whom a second surgical procedure would be high risk (i.e., those with prior radiation therapy or a porcelain aorta). In patients with shortened longevity and/or multiple comorbidities, a bioprosthesis would be most appropriate. In women who desire subsequent pregnancy, the issue of anticoagulation during pregnancy is an additional consideration (Section 13 in the 2014 VHD guideline). The availability of transcatheter valve-in-valve replacement is changing the dynamics of the discussion of the trade-offs between mechanical and bioprosthetic valves, but extensive long-term follow-up of transcatheter valves is not yet available, and not all bioprostheses are suitable for a future valve-in-valve procedure (152-154). A valve-in-valve procedure will always require insertion of a valve smaller than the original bioprosthesis, and patient-prosthesis mismatch is a potential problem, depending on the size of the initial prosthesis. Irrespective of whether a mechanical valve or bioprosthesis is placed, a root enlargement should be considered in patients with a small annulus to ensure that there is not an initial patient-prosthesis mismatch.

I	C	<b>A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.</b>	2014 recommendation remains current.
---	---	---	--------------------------------------

IIa	B-NR	<b>An aortic or mitral mechanical prosthesis is reasonable for patients less than 50 years of age who do not have a contraindication to anticoagulation (141,149,151,155-157).</b>	<b>MODIFIED:</b> LOE updated from B to B-NR. The age limit for mechanical prosthesis was lowered from 60 to 50 years of age.
-----	------	--	--

See Online Data Supplement 20  
(Updated From 2014 VHD Guideline)

Patients <50 years of age at the time of valve implantation incur a higher and earlier risk of bioprosthetic valve deterioration (141,149,151,155-157). 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 (151). Anticoagulation with a VKA can be accomplished with acceptable risk in the majority of patients <50 years of age, particularly in compliant patients with appropriate monitoring of International Normalized Ratio (INR) levels. Thus, the balance between valve durability versus 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. (See the first Class I recommendation for additional discussion).

IIa	B-NR	<b>For patients between 50 and 70 years of age, it is reasonable to individualize the choice of either a mechanical or bioprosthetic valve prosthesis on the basis of individual patient factors and preferences, after full discussion of the trade-offs involved (141-145,157-160).</b>	<b>MODIFIED:</b> Uncertainty exists about the optimum type of prosthesis (mechanical or bioprosthetic) for patients 50 to 70 years of age. There are conflicting data on survival benefit of mechanical versus bioprosthetic valves in this age group, with equivalent stroke and thromboembolic outcomes. Patients receiving a mechanical valve incur greater risk of bleeding, and those undergoing bioprosthetic valve replacement more often require repeat valve surgery.
-----	------	---	--

See Online Data Supplement 20  
(Updated From 2014 VHD Guideline)

Uncertainty and debate continue about which type of prosthesis is appropriate for patients 50 to 70 years of age. RCTs incorporating most-recent-generation valve types are lacking. Newer-generation tissue prostheses 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 (147,149-151,161). The risks of bleeding and thromboembolism with mechanical prostheses are now low, especially in compliant patients with appropriate INR monitoring. Observational and propensity-matched data vary, and valve-in-valve technology has not previously been incorporated into rigorous decision analysis. Several studies have shown a survival advantage with a mechanical prosthesis in this age group (142,157-159). Alternatively, large retrospective observational studies have shown similar long-term survival in patients 50 to 69 years of age undergoing mechanical versus bioprosthetic valve replacement (143-145,160). In general, patients with mechanical valve replacement experience a higher risk of bleeding due to anticoagulation, whereas individuals who receive a bioprosthetic valve replacement experience a higher rate of reoperation due to structural deterioration of the prosthesis and perhaps a decrease in survival (142,143,145-160,162). Stroke rate appears to be similar in patients undergoing either mechanical or bioprosthetic AVR, but it is higher with mechanical than with bioprosthetic MVR (142-145,157). There are several other factors to consider in the choice of type of valve prosthesis (Table 3). Ultimately, the choice of mechanical versus bioprosthetic valve replacement for all patients, but especially for those between 50 and 70 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 (143,145-160,162).

(continued)

IIa	B	A bioprosthesis is reasonable for patients more than 70 years of age (163-166).	2014 recommendation remains current.
IIb	C	Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered for young patients when VKA anticoagulation is contraindicated or undesirable (167-169).	2014 recommendation remains current.

**TABLE 3 Factors Used for Shared Decision Making About Type of Valve Prosthesis**

Favor Mechanical Prosthesis	Favor Bioprosthesis
Age <50 y	Age >70 y
<ul style="list-style-type: none"> <li>■ Increased incidence of structural deterioration with bioprosthesis (15-y risk: 30% for age 40 y, 50% for age 20 y)</li> <li>■ Lower risk of anticoagulation complications</li> </ul>	<ul style="list-style-type: none"> <li>■ Low incidence of structural deterioration (15-y risk: &lt;10% for age &gt;70 y)</li> <li>■ Higher risk of anticoagulation complications</li> </ul>
Patient preference (avoid risk of reintervention)	Patient preference (avoid risk and inconvenience of anticoagulation and absence of valve sounds)
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 (e.g., AF)	Access to surgical centers with low reoperation mortality rate
High-risk reintervention (e.g., porcelain aorta, prior radiation therapy)	
Small aortic root size for AVR (may preclude valve-in-valve procedure in future).	

AF indicates atrial fibrillation; AVR, aortic valve replacement; INR, International Normalized Ratio; and VKA, vitamin K antagonist.

## 11.2. Antithrombotic Therapy for Prosthetic Valves

### 11.2.1. Diagnosis and Follow-Up

Effective oral antithrombotic therapy in patients with mechanical heart valves requires continuous VKA anticoagulation with an INR in the target range. 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. In addition, fluctuations in INR are associated with an increased incidence of complications in patients with prosthetic heart valves, so patients and caregivers should strive to attain the specific INR value (170,171). The effects of VKA anticoagulation vary with the specific drug, absorption, various foods, alcohol, other medications,

and changes in liver function. Most of the published studies of VKA therapy used warfarin, although other coumarin agents are used on a worldwide basis. In clinical practice, a program of patient education and close surveillance by an experienced healthcare professional, with periodic INR determinations, is necessary. Patient monitoring through dedicated anticoagulation clinics results in lower complication rates than those seen with standard care and is cost effective because of lower rates of bleeding and hemorrhagic complications (172,173). Periodic direct patient contact and telephone encounters (174) with the anticoagulation clinic pharmacists (175,176) or nurses are equally effective in reducing complication rates (177). Self-monitoring with home INR measurement devices is another option for educated and motivated patients.

### 11.2.2. Medical Therapy: Recommendations

## Recommendations for Antithrombotic Therapy for Patients with Prosthetic Heart Valves

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	A	Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve (178-183).	2014 recommendation remains current.



(continued)



Anticoagulation with a VKA to achieve an INR of 2.5 is recommended for patients with a mechanical bileaflet or current-generation single-tilting disc AVR and no risk factors for thromboembolism (178,184-186).

2014 recommendation remains current.



Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage) (178).

2014 recommendation remains current.



Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR (178,187,188).

2014 recommendation remains current.



Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (178,189,190).

2014 recommendation remains current.



Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve (178,191-194).

2014 recommendation remains current.



See Online Data Supplement 6.

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 bioprosthetic MVR or AVR in patients at low risk of bleeding (195-197).

**MODIFIED:** LOE updated from C to B-NR. Anticoagulation for all surgical tissue prostheses was combined into 1 recommendation, with extension of the duration of anticoagulation up to 6 months. Stroke risk and mortality rate are lower in patients who receive anticoagulation for up to 6 months after implantation of a tissue prosthesis than in those who have do not have anticoagulation. Anticoagulation for a tissue prosthesis is also supported by reports of valve thrombosis for patients undergoing bioprosthetic surgical AVR or MVR, a phenomenon that may be warfarin responsive.

Many patients who undergo implantation of a surgical bioprosthetic MVR or AVR will not require life-long anticoagulation. However, there is an increased risk of ischemic stroke early after operation, particularly in the first 90 to 180 days after operation with either a bioprosthetic AVR or MVR (198-205). 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 MVR who received anticoagulation had a lower rate of thromboembolism than those who did not receive therapy with VKA (2.5% per year with anticoagulation versus 3.9% per year without anticoagulation;  $p=0.05$ ) (193). Even with routine anticoagulation early after valve surgery, the incidence of ischemic stroke within the first 30 postoperative days was higher after replacement with a biological prosthesis (4.6%±1.5%) than after mitral valve repair (1.5%±0.4%) or replacement with a mechanical prosthesis (1.3%±0.8%;  $p<0.001$ ) (206). Small RCTs have not established a convincing net benefit of anticoagulation after implantation of a bioprosthetic AVR (205,207); however, a large observational Danish registry demonstrated a lower risk of stroke and death with VKA extending up to 6 months, without a significantly increased bleeding risk (197). Concern has also been raised about a higher-than-recognized incidence of bioprosthetic valve thrombosis leaflets after surgical valve replacement (196). Thus, anticoagulation with an INR target of 2.5 may be reasonable for at least 3 months and perhaps for as long as 6 months after implantation of a surgical bioprosthetic MVR or AVR in patients at low risk of bleeding. Compared with oral anticoagulation alone, the addition of dual-antiplatelet therapy results in at least a 2- to 3-fold increase in bleeding complications, and the recommendations on triple therapy should be followed (208).



See Online Data Supplement 6.

A lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors (209).

**NEW:** A lower target INR was added for patients with a mechanical On-X AVR and no thromboembolic risk factors treated with warfarin and low-dose aspirin. A single RCT of lower- versus standard-intensity anticoagulation in patients undergoing On-X AVR showed equivalent outcomes, but the bleeding rate in the control group was unusually high.

(continued)

In patients without risk factors who receive a mechanical On-X aortic heart valve (On-X Life Technologies Inc., Austin, Texas), a lower INR target of 1.5 to 2.0 (in conjunction with aspirin 81 mg daily) may be considered for long-term management, beginning 3 months after surgery. Warfarin dosing is targeted to an INR of 2.5 (range 2.0 to 3.0) for the first 3 months after surgery (209). This is based on a single RCT of lower- versus standard-intensity anticoagulation in patients undergoing On-X AVR, showing equivalent outcomes. The control arm did have a bleeding rate of 3.2% per patient-year (209).

IIb	B-NR	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding (203,210,211).	<b>NEW:</b> Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by multidetector computerized tomographic scanning. This valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA.
-----	------	---	--

See Online Data Supplement 6.

Several studies have demonstrated the occurrence of prosthetic valve thrombosis after TAVR, as assessed by multidetector computerized tomography, which shows reduced leaflet motion and hypo-attenuating opacities. The incidence of this finding has varied from 7% to 40%, depending on whether the patients are from a clinical trial or registry and whether some patients received anticoagulation with VKA (203,210,211). Up to 18% of patients with a thrombus formation developed clinically overt obstructive valve thrombosis (210). A post-TAVR antithrombotic regimen without warfarin seems to predispose patients to the development of valve thrombosis (203,210). The utility of the DOACs in this population is unknown at this time.

IIb	C	Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.	2014 recommendation remains current.
-----	---	---	--------------------------------------

III: Harm	B	Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses (200,212,213).	2014 recommendation remains current.
-----------	---	---	--------------------------------------

### 11.3. Bridging Therapy for Prosthetic Valves

#### 11.3.1. Diagnosis and Follow-Up

The management of patients with mechanical heart valves for whom interruption of anticoagulation therapy

is needed for diagnostic or surgical procedures should take into account the type of procedure; bleeding risk; patient risk factors; and type, location, and number of heart valve prostheses.

#### 11.3.2. Medical Therapy: Recommendations

### Recommendations for Bridging Therapy for Prosthetic Valves

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	C	Continuation of VKA anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled.	2014 recommendation remains current.
I	C	Temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures.	2014 recommendation remains current.
IIa	C-LD	Bridging anticoagulation therapy during the time interval when the INR is subtherapeutic preoperatively is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR (199,214,215).	<b>MODIFIED:</b> COR updated from I to IIa, LOE updated from C to C-LD. RCTs of bridging anticoagulant therapy versus no bridging therapy for patients with AF who do not have a mechanical heart valve have shown higher risk of bleeding without a change in incidence of thromboembolic events. This may have implications for bridging anticoagulation therapy for patients with prosthetic valves.

See Online Data Supplement 21  
 (Updated From 2014 VHD Guideline)

(continued)

"Bridging" therapy with either intravenous unfractionated heparin or low-molecular-weight heparin has evolved empirically to reduce thromboembolic events during temporary interruption of oral anticoagulation in higher-risk patients, such as those with a mechanical MVR or AVR and additional risk factors for thromboembolism (e.g., AF, previous thromboembolism, hypercoagulable condition, older-generation mechanical valves [ball-cage or tilting disc], LV systolic dysfunction, or >1 mechanical valve) (214).

When interruption of oral VKA therapy is deemed necessary, the agent is usually stopped 3 to 4 days before the procedure (so the INR falls to <1.5 for major surgical procedures) and is restarted postoperatively as soon as bleeding risk allows, typically 12 to 24 hours after surgery. Bridging anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin is started when the INR falls below the therapeutic threshold (i.e., 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 unfractionated heparin) or 12 hours (for subcutaneous low-molecular-weight heparin) 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 needing temporary interruption of oral anticoagulant therapy, although such studies are ongoing. The evidence used to support bridging therapy derives from cohort studies with poor or no comparator groups (214,215). 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 (199). Accordingly, decisions about bridging should be individualized and should account for the trade-offs between thrombosis and bleeding.

IIa	C	Administration of fresh frozen plasma or prothrombin complex concentrate is reasonable in patients with mechanical valves receiving VKA therapy who require emergency noncardiac surgery or invasive procedures.	2014 recommendation remains current.
-----	---	--	--------------------------------------

## 11.6. Acute Mechanical Prosthetic Valve Thrombosis

### 11.6.1. Diagnosis and Follow-Up: Recommendation

#### Recommendation for Mechanical Prosthetic Valve Thrombosis Diagnosis and Follow-Up

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	B-NR	Urgent evaluation with multimodality imaging is indicated in patients with suspected mechanical prosthetic valve thrombosis to assess valvular function, leaflet motion, and the presence and extent of thrombus (216-222).	<b>MODIFIED:</b> LOE updated to B-NR. Multiple recommendations for imaging in patients with suspected mechanical prosthetic valve thrombosis were combined into a single recommendation. Multimodality imaging with transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), fluoroscopy, and/or computed tomography (CT) scanning may be more effective than one imaging modality alone in detecting and characterizing valve thrombosis. Different imaging modalities are necessary because valve function, leaflet motion, and extent of thrombus should all be evaluated.

See Online Data Supplement 7.

Obstruction of mechanical prosthetic heart valves may be caused by thrombus formation, pannus ingrowth, or a combination of both (216). The presentation can vary from mild dyspnea to severe acute pulmonary edema. Urgent diagnosis, evaluation, and therapy are indicated because rapid deterioration can occur if there is thrombus causing malfunction of leaflet opening. The examination may demonstrate a stenotic murmur and muffled closing clicks, and further diagnostic evaluation is required. TTE and/or TEE should be performed to examine valve function and the status of the left ventricle (216). Leaflet motion should be visualized with TEE (particularly for a mitral prosthesis) or with CT or fluoroscopy (for an aortic prosthesis) (217-223). Prolonged periods of observation under fluoroscopy or TEE may be required to diagnose intermittent obstruction. The presence and quantification of thrombus should be evaluated by either TEE or CT (217,223). Differentiation of valve dysfunction due to thrombus versus fibrous tissue ingrowth (pannus) is challenging because the clinical presentations are similar. Thrombus is more likely with a history of inadequate anticoagulation, a more acute onset of valve dysfunction, and a shorter time between surgery and symptoms. Mechanical prosthetic valve thrombosis is diagnosed by an abnormally elevated gradient across the prosthesis, with either limited leaflet motion or attached mobile densities consistent with thrombus, or both. Vegetations from IE must be excluded. If obstruction is present with normal leaflet motion and no thrombus, either patient-prosthesis mismatch or pannus formation is present (or both). Thrombus formation on the valve in the absence of obstruction can also occur and is associated with an increased risk of embolic events.

11.6.3. Intervention: Recommendation

mor-

**Recommendation for Mechanical Prosthetic Valve Thrombosis Intervention**

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	B-NR	Urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery is recommended for patients with a thrombosed left-sided mechanical prosthetic heart valve presenting with symptoms of valve obstruction (224-231).	<b>MODIFIED:</b> LOE updated to B-NR. Multiple recommendations based only on NYHA class symptoms were combined into 1 recommendation. Slow-infusion fibrinolytic therapy has higher success rates and lower complication rates than prior high-dose regimens and is effective in patients previously thought to require urgent surgical intervention. The decision for emergency surgery versus fibrinolytic therapy should be based on multiple factors, including the availability of surgical expertise and the clinical experience with both treatments.

See Online Data Supplement 7 and 7A.

Mechanical left-sided prosthetic valve obstruction is a serious complication with high mortality and morbidity and requires urgent therapy with either fibrinolytic therapy or surgical intervention. There has not been an RCT comparing the 2 interventions, and the literature consists of multiple case reports, single-center studies, multicenter studies, registry reports, and meta-analyses—with all the inherent problems of differing definitions of initial diagnosis, fibrinolytic regimens, and surgical expertise (224-235) (Data Supplement 7A). 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/II symptoms (225,226,232-234). The results of fibrinolytic therapy before 2013 showed an overall 30-day mortality rate of 7% and hemodynamic success rate of 75% but a thromboembolism rate of 13% and major bleeding rate of 6% (intracerebral hemorrhage, 3%) (224-230). However, recent reports using an echocardiogram-guided slow-infusion low-dose fibrinolytic protocol have shown success rates >90%, with embolic event rates <2% and major bleeding rates <2% (231,235). This fibrinolytic therapy regimen can be successful even in patients with advanced NYHA class and larger-sized thrombi. On the basis of these findings, the writing group recommends urgent initial therapy for prosthetic mechanical valve thrombosis resulting in symptomatic obstruction, but the decision for surgery versus fibrinolysis is dependent on individual patient characteristics that would support the recommendation of one treatment over the other, as shown in Table 4, as well as the experience and capabilities of the institution. All factors must be taken into consideration in a decision about therapy, and the decision-making process shared between the caregiver and patient. Final definitive plans should be based on the initial response to therapy.

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-III
Large clot (>0.8 cm <sup>2</sup> )	Small clot (≤0.8 cm <sup>2</sup> )
Left atrial thrombus	No left atrial 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.

**11.7. Prosthetic Valve Stenosis**

Surgical reoperation to replace the stenotic prosthetic heart valve has been the mainstay treatment modality. Although it is associated with acceptable mortality and

morbidity in the current era, it remains a serious clinical event and carries a higher risk than the initial surgery. Reoperation is usually required for moderate-to-severe prosthetic dysfunction (structural and nonstructural), dehiscence, and prosthetic valve endocarditis. Reoperation may also be needed for recurrent thromboembolism, severe intravascular hemolysis, severe recurrent bleeding from anticoagulant therapy, and thrombosed prosthetic valves. In 2015, catheter-based therapy with transcatheter valve-in-valve emerged as an acceptable alternative to treat high- and extreme-risk patients with bioprosthetic aortic valve stenosis (stenosis, insufficiency, or combined) in the absence of active IE (154).

Symptomatic prosthetic valve stenosis secondary to thrombosis is observed predominantly with mechanical valves. Mechanical prosthetic valve thrombosis and its treatment are discussed in Section 11.6. Bioprosthetic valve thrombosis can result in thromboembolic events or obstruction. In a pooled analysis from 3 studies including 187 patients who underwent either TAVR or bioprosthetic surgical AVR, reduced leaflet motion was noted on 4-dimensional volume-rendered CT imaging in 21% of patients (203). In this small cohort, therapeutic

anticoagulation with warfarin was associated with lower incidence of reduced leaflet motion than that associated with dual antiplatelet therapy, as well as more restoration of leaflet motion on follow-up CT imaging. Subclinical leaflet thrombosis was identified as the likely cause on the basis of advanced and characteristic imaging findings (203). As outlined by the U.S. Food and Drug Administration, most cases of reduced leaflet motion (which occurs in 10% to 40% of TAVR patients and 8% to 12% of surgical AVR patients) were discovered by advanced imaging studies in asymptomatic patients (236). The diagnosis of bioprosthetic valve thrombosis remains difficult, with most suspected bioprosthetic valve thrombosis based on increased transvalvular gradients.

In some patients, the size of the prosthetic valve that can be implanted results in inadequate blood flow to meet the metabolic demands of the patient, even when the prosthetic valve itself is functioning normally. This situation, called *patient-prosthesis mismatch* (defined as an indexed effective orifice area  $\leq 0.85$  cm<sup>2</sup>/m<sup>2</sup> for aortic

valve prostheses), is a predictor of a high transvalvular gradient, persistent LV hypertrophy, and an increased rate of cardiac events after AVR (237,238). The impact of a relatively small valve area is most noticeable with severe patient-prosthesis mismatch, defined as an indexed orifice area  $< 0.65$  cm<sup>2</sup>/m<sup>2</sup>. Patient-prosthesis mismatch is especially detrimental in patients with reduced LVEF and may decrease the likelihood of resolution of symptoms and improvement in LVEF. Patient-prosthesis mismatch can be avoided or reduced by choice of a valve prosthesis that will have an adequate indexed orifice area, determined by the patient's body size and annular dimension. In some cases, annular enlargement or other approaches may be needed to allow implantation of an appropriately sized valve or avoidance of a prosthetic valve. With bileaflet mechanical valves, patterns of blood flow are complex, and significant pressure recovery may be present; this may result in a high velocity across the prosthesis that should not be mistaken for prosthetic valve stenosis or patient-prosthesis mismatch, particularly in those with small aortic diameters.

### 11.7.3. Intervention: Recommendation

#### Recommendations for Prosthetic Valve Stenosis

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	C	Repeat valve replacement is indicated for severe symptomatic prosthetic valve stenosis (239-241).	2014 recommendation remains current.
IIa	C-LD	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 (203,242-246). <small>See Online Data Supplement 8.</small>	<b>NEW:</b> Case series of patients presenting with bioprosthetic valve stenosis have suggested improvement in hemodynamics with VKA treatment because of resolution of thrombus on the valve leaflets.

There are no medical therapies known to prevent or treat bioprosthetic valve degeneration. However, bioprosthetic valve thrombosis may present with slowly progressive stenosis months to years after implantation. Small, nonrandomized studies support the use of VKAs to treat patients with bioprosthetic valve thrombosis after both surgical AVR and TAVR (203,242-246). In a retrospective single-center report of 31 patients with bioprosthetic valve thrombosis who were initially treated with either a VKA or surgery/thrombolysis, VKA-treated patients had 87% thrombus resolution and experienced hemodynamic and clinical improvement comparable to surgery/thrombolysis, with no complications (244). Notably, in that case series, the peak incidence of bioprosthetic valve thrombosis occurred 13 to 24 months after implantation, with the longest interval being 6.5 years (244). Surgery or thrombolysis may still be needed for patients who are hemodynamically unstable or have advanced and refractory HF, large mobile thrombus, or high risk of embolism. At present, the DOACs have not been adequately studied, nor has the U.S. Food and Drug Administration approved them for prophylaxis or treatment of prosthetic valve thrombosis.

IIa	B-NR	For severely symptomatic patients with bioprosthetic aortic valve stenosis judged by the heart team to be at high or prohibitive risk of reoperation, and in whom improvement in hemodynamics is anticipated, a transcatheter valve-in-valve procedure is reasonable (154,247,248). <small>See Online Supplement 9.</small>	<b>NEW:</b> Registries and case series have reported on the short-term outcomes and complication rates in patients with bioprosthetic AS who have undergone transcatheter valve-in-valve therapy.
-----	------	--	---

(continued)

The VIVID (Valve-In-Valve International Data) Registry is the largest registry to date examining outcomes of the transcatheter valve-in-valve procedure in 459 patients, of whom about 40% had isolated stenosis and 30% had combined regurgitation and stenosis (154). Within 1 month after the valve-in-valve procedure, 7.6% of patients died, 1.7% had a major stroke, and 93% of survivors experienced good functional status (NYHA class I/II). The overall 1-year survival rate was 83.2% (154). In nonrandomized studies and a systematic review comparing outcomes and safety of the transcatheter valve-in-valve procedure with repeat surgical AVR, the valve-in-valve procedure was found to have similar hemodynamic outcomes, lower stroke risk, and reduced bleeding risk as compared with repeat surgery (248). No data are available yet on the durability and long-term outcomes after transcatheter valve-in-valve procedures. There are also unique clinical and anatomic challenges, requiring experienced operators with an understanding of the structural and fluoroscopic characteristics of the failed bioprosthetic valve. An anticipated hemodynamic improvement from the transcatheter valve-in-valve procedure occurs only in patients with larger-sized prostheses, because a smaller-sized valve will always be placed within a failing bioprosthesis. In 2015, the U.S. Food and Drug Administration approved the transcatheter heart valve-in-valve procedure for patients with symptomatic heart disease due to stenosis of a surgical bioprosthetic aortic valve who are at high or greater risk for open surgical therapy (as judged by a heart team, including a cardiac surgeon) (249). The transcatheter aortic valve-in-valve procedure is not currently approved to treat para-prosthetic valve regurgitation or for failed/degenerated transcatheter heart valves; and it is contraindicated in patients with IE. Transcatheter valve-in-valve implantation has also been successfully performed for failed surgical bioprostheses in the mitral, pulmonic, and tricuspid positions.

## 11.8. Prosthetic Valve Regurgitation

### 11.8.3. Intervention: Recommendations

#### Recommendations for Prosthetic Valve Regurgitation

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B	Surgery is recommended for operable patients with mechanical heart valves with intractable hemolysis or HF due to severe prosthetic or paraprosthetic regurgitation (250,251).	2014 recommendation remains current.
IIa	C-LD	Surgery is reasonable for asymptomatic patients with severe bioprosthetic regurgitation if operative risk is acceptable (241).  <small>See Online Data Supplement 23 (Updated From 2014 VHD Guideline)</small>	<b>MODIFIED:</b> LOE updated from C to C-LD. A specific indication for surgery is the presence of severe bioprosthetic regurgitation in a patient with acceptable operative risk. With the new recommendation for valve-in-valve therapy, indications for intervention need to account for patients who would benefit from surgery versus those who would benefit from transcatheter therapy, determined by type of valve, symptomatic status, and risk of reoperation.
IIa	B	Percutaneous repair of paravalvular regurgitation is reasonable in patients with prosthetic heart valves and intractable hemolysis or NYHA class III/IV HF who are at high risk for surgery and have anatomic features suitable for catheter-based therapy when performed in centers with expertise in the procedure (252-254).	2014 recommendation remains current.
IIa	B-NR	For severely symptomatic patients with bioprosthetic aortic valve regurgitation judged by the heart team to be at high or prohibitive risk for surgical therapy, in whom improvement in hemodynamics is anticipated, a transcatheter valve-in-valve procedure is reasonable (154,247,248).  <small>See Online Data Supplement 9.</small>	<b>NEW:</b> Registries and case series of patients have reported on the short-term outcomes and complication rates for patients with bioprosthetic aortic regurgitation who have undergone transcatheter valve-in-valve replacement.

Bioprosthetic valve degeneration can result in regurgitation due to leaflet calcification and noncoaptation or leaflet degeneration with a tear or perforation. Even in asymptomatic patients with severe bioprosthetic regurgitation, valve replacement is reasonable because of the risk of sudden clinical deterioration if further leaflet tearing occurs (241). The increased risk of a repeat operation must always be taken into consideration. The type of valve prosthesis and method of replacement selected for a patient undergoing reoperation depend on the same factors as those for patients undergoing a first valve replacement.

(continued)

The VIVID (Valve-In-Valve International Data) Registry is the largest registry to date examining outcomes of the transcatheter valve-in-valve procedure in 459 patients, of whom 30% had severe prosthetic valve regurgitation and 30% had combined regurgitation and stenosis (154). Within 1 month after the valve-in-valve procedure, 7.6% of patients died, 1.7% had a major stroke, and 93% of survivors experienced good functional status (NYHA class I/II). The overall 1-year survival rate was 83.2% (154). In nonrandomized studies and a systematic review comparing outcomes and safety of the transcatheter valve-in-valve procedure with repeat surgical AVR, the valve-in-valve procedure was found to have similar hemodynamic outcomes, lower stroke risk, and reduced bleeding risk as compared with repeat surgery (248). No data are available yet on the durability and long-term outcomes after transcatheter valve-in-valve procedures. There are also unique clinical and anatomic challenges requiring experienced operators with an understanding of the structural and fluoroscopic characteristics of the failed bioprosthetic valve. The use of transcatheter valve-in-valve procedures to treat bioprosthetic valve regurgitation should be applied only to patients with larger-sized prostheses for whom hemodynamic improvement is anticipated. The transcatheter aortic valve-in-valve procedure is not currently approved to treat paraprosthetic valve regurgitation or failed/degenerated transcatheter heart valves, and it is contraindicated in patients with IE. Transcatheter valve-in-valve implantation has also been successfully performed for failed surgical bioprostheses in the mitral, pulmonic, and tricuspid positions.

## 12. INFECTIVE ENDOCARDITIS

### 12.2. Infective Endocarditis

#### 12.2.3. Intervention: Recommendations

#### Recommendations for IE Intervention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	B	Decisions about timing of surgical intervention should be made by a multispecialty Heart Valve Team of cardiology, cardiothoracic surgery, and infectious disease specialists (255).	2014 recommendation remains current.
I	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE who present with valve dysfunction resulting in symptoms of HF (256-261).	2014 recommendation remains current.
I	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with left-sided IE caused by <i>S. aureus</i> , fungal, or other highly resistant organisms (261-268).	2014 recommendation remains current.
I	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (261,269-273).	2014 recommendation remains current.
I	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) for IE is indicated in patients with evidence of persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy (261,263,268,274-276).	2014 recommendation remains current.
I	C	Surgery is recommended for patients with prosthetic valve endocarditis and relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequently negative blood cultures) without other identifiable source for portal of infection.	2014 recommendation remains current.

(continued)

I	B	Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is indicated as part of the early management plan in patients with IE with documented infection of the device or leads (277-280).	2014 recommendation remains current.
IIa	B	Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients with valvular IE caused by <i>S. aureus</i> or fungi, even without evidence of device or lead infection (277-280).	2014 recommendation remains current.
IIa	C	Complete removal of pacemaker or defibrillator systems, including all leads and the generator, is reasonable in patients undergoing valve surgery for valvular IE.	2014 recommendation remains current.
IIa	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is reasonable in patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy (281-283).	2014 recommendation remains current.
IIb	B	Early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered in patients with native valve endocarditis who exhibit mobile vegetations greater than 10 mm in length (with or without clinical evidence of embolic phenomenon) (281-283).	2014 recommendation remains current.
IIb	B-NR	Operation without delay may be considered 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 (284,285).	<b>NEW:</b> The risk of postoperative neurological deterioration is low after a cerebral event that has not resulted in extensive neurological damage or intracranial hemorrhage. If surgery is required after a neurological event, recent data favor early surgery for better overall outcomes.
<p>Stroke is an independent risk factor for postoperative death in IE patients. 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 &gt;4 weeks after stroke (284). 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 1 week of a stroke than in patients who underwent surgery ≥8 days after a stroke (285).</p>			
IIb	B-NR	Delaying valve surgery for at least 4 weeks may be considered for patients with IE and major ischemic stroke or intracranial hemorrhage if the patient is hemodynamically stable (286).	<b>NEW:</b> In patients with extensive neurological damage or intracranial hemorrhage, cardiac surgery carries a high risk of death if performed within 4 weeks of a hemorrhagic stroke.
<p>Patients with hemorrhagic stroke and IE have a prohibitively high surgical risk for at least 4 weeks after the hemorrhagic event. One multicenter observational study (286) 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 bleeds postoperatively 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 (286).</p>			



## PRESIDENTS AND STAFF

### American College of Cardiology

Richard A. Chazal, MD, FACC, President  
Shalom Jacobovitz, Chief Executive Officer  
William J. Oetgen, MD, MBA, FACC, Executive Vice President,  
Science, Education, Quality, and Publishing  
Amelia Scholtz, PhD, Publications Manager, Science,  
Education, Quality, and Publishing

### American College of Cardiology/American Heart Association

Katherine Sheehan, PhD, Director, Guideline Strategy and Operations

Lisa Bradfield, CAE, Director, Guideline Methodology and Policy

Abdul R. Abdullah, MD, Science and Medicine Advisor  
Clara Fitzgerald, Project Manager, Clinical Practice Guidelines  
**American Heart Association**

Steven R. Houser, PhD, FAHA, President  
Nancy Brown, Chief Executive Officer  
Rose Marie Robertson, MD, FAHA, Chief Science and Medicine Officer  
Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations  
Jody Hundley, Production Manager, Scientific Publications, Office of Science Operations

## REFERENCES

- Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). *Clinical Practice Guidelines We Can Trust*. ed. Washington, DC: Press NA, 2011.
- Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). *Finding What Works in Health Care: Standards for Systematic Reviews*. ed. Washington, DC: Press NA, 2011.
- 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. *J Am Coll Cardiol*. 2014;63:2304-22.
- 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: [http://assets.cardiosource.com/Methodology\\_Manual\\_for\\_ACC\\_AHA\\_Writing\\_Committees.pdf](http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf). Accessed February 2017.
- Halperin JL, Levine GN, Al-Khatib SM, Birtcher K, Bozkurt B. 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. *J Am Coll Cardiol*. 2016;67:1572-4.
- Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:213-65.
- Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:1373-84.
- Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. 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. *J Am Coll Cardiol*. 2014;64:1851-6.
- Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438-88.
- Nishimura R, 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. *J Am Coll Cardiol*. 2014;63:e57-185.
- 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.
- 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;36:3075-128.
- Glenny AM, Oliver R, Roberts GJ, Hooper L, Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database Syst Rev*. 2013;CD003813.
- (NICE) UNIFHaCE. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. Available at: <https://www.nice.org.uk/guidance/cg64>. Accessed January 20, 2017.
- Mougeot FKB, Saunders SE, Brennan MT, Lockhart PB. 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.
- 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.
- Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. *Lancet*. 2015;385:1219-28.
- 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.
- 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.
- 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.
- 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.
- Strom BL, Abrutyn E, Berlin JA, et al. Risk factors for infective endocarditis: oral hygiene and nonoral exposures. *Circulation*. 2000;102:2842-8.
- 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.
- Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation*. 2008;117:3118-25.
- Geist SM, Fitzpatrick S, Geist JR. American Heart Association 2007 guidelines on prevention of infective endocarditis. *J Mich Dent Assoc*. 2007;89:50-6.
- 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.

27. The 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;36:3036-7.
28. Horstkotte D, Rosen H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. *Eur Heart J*. 1987;8 suppl J: 379-81.
29. 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.
30. Amat-Santos JJ, 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.
31. 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.
32. Karavas AN, Filsoufi F, Mihaljevic T, Aranki SF, Cohn LH, Byrne JG. Risk factors and management of endocarditis after mitral valve repair. *J Heart Valve Dis*. 2002;11:660-4.
33. Gillinov AM, Faber CN, Sabik JF, et al. Endocarditis after mitral valve repair. *Ann Thorac Surg*. 2002;73: 1813-6.
34. Pérez-Gómez F, Alegría E, Berjón J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and non-valvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol*. 2004;44:1557-66.
35. Noseworthy PA, Yao X, Shah ND, Gersh BJ. 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.
36. 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.
37. 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.
38. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). *Circulation*. 2016;134:589-98.
39. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005:CD001927.
40. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
41. Lytvyn 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.
42. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988;9 Suppl E: 57-64.
43. 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.
44. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005;111:3316-26.
45. Kvidal P, Bergström R, Hörte LG, Ståhle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol*. 2000;35:747-56.
46. Murphy ES, Lawson RM, Starr A, Rahimtoola SH. 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.
47. Rosenhek R. Aortic stenosis: disease severity, progression, timing of intervention and role in monitoring transcatheter valve implantation. In: Otto CM, editor. *The Practice of Clinical Echocardiography*. 4 ed. Philadelphia, PA: Elsevier/Saunders, 2012:425-49.
48. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. *Circulation*. 1982;66:1105-10.
49. 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.
50. 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.
51. Deeb GM, Reardon MJ, Chetcuti S, et al. Three-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2565-74.
52. Holmes DR Jr., Nishimura RA, Grover FL, et al. Annual Outcomes With Transcatheter Valve Therapy: From the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2015;66:2813-23.
53. 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.
54. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-98.
55. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (French Aortic National CoreValve and Edwards) registry. *Eur Heart J*. 2011;32:191-7.
56. Rodés-Cabau J, Webb JG, Cheung A, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol*. 2012;60:1864-75.
57. Abdel-Wahab M, Neumann FJ, Mehilli J, et al. One-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.
58. 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.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. Siemieniuk RA, Agoristas 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.
65. 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.
66. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ*. 2016;354:i5085.
67. 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.
68. 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.
69. 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.
70. Goldstein D, Moskowitz AJ, Gelijs AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med*. 2016;374:344-53.
71. 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.
72. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178-88.
73. David TE, Armstrong S, McCrindle BW, Manthot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation*. 2013; 127:1485-92.
74. 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.
- 75.** 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.
- 76.** Crawford MH, Soucek J, Oprian 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.
- 77.** 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.
- 78.** Grigioni F, Enriquez-Sarano M, Ling LH, et al. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol.* 1999;34:2078-85.
- 79.** Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. *J Am Coll Cardiol Img.* 2008;1:133-41.
- 80.** Schuler G, Peterson KL, Johnson A, et al. Temporal response of left ventricular performance to mitral valve surgery. *Circulation.* 1979;59:1218-31.
- 81.** Starling MR. Effects of valve surgery on left ventricular contractile function in patients with long-term mitral regurgitation. *Circulation.* 1995;92:811-8.
- 82.** 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.
- 83.** STS online risk calculator. Available at: <http://riskcalc.org/stswebriskcalc> Accessed January 20, 2017.
- 84.** Braunberger E, Deloche A, Berrebi A, et al. Very long-term results (more than 20 years) of valve repair with Carpentier's techniques in nonrheumatic mitral valve insufficiency. *Circulation.* 2001;104:18-11.
- 85.** Cohn LH. Surgery for mitral regurgitation. *JAMA.* 1988;260:2883-7.
- 86.** Cosgrove DM, Chavez AM, Lytle BW, et al. Results of mitral valve reconstruction. *Circulation.* 1986;74:182-7.
- 87.** David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. *Circulation.* 1983;68:1176-82.
- 88.** David TE, Burns RJ, Bacchus CM, Druck MN. Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae. *J Thorac Cardiovasc Surg.* 1984;88:718-25.
- 89.** David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. 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.
- 90.** Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg.* 2009;87:1431-7; discussion 7-349.
- 91.** Goldman KE. Dental management of patients with bone marrow and solid organ transplantation. *Dent Clin North Am.* 2006;50:659-76, viii.
- 92.** Hansen DE, Sarris GE, Niczyporuk MA, Derby GC, Cahill PD, Miller DC. Physiologic role of the mitral apparatus in left ventricular regional mechanics, contraction synergy, and global systolic performance. *J Thorac Cardiovasc Surg.* 1989;97:521-33.
- 93.** Hennein HA, Swain JA, McIntosh CL, Bonow RO, Stone CD, Clark RE. Comparative assessment of chordal preservation versus chordal resection during mitral valve replacement. *J Thorac Cardiovasc Surg.* 1990;99:828-36; discussion 36-37.
- 94.** Horskotte D, Schulte HD, Bircks W, Strauer BE. The effect of chordal preservation on late outcome after mitral valve replacement: a randomized study. *J Heart Valve Dis.* 1993;2:150-8.
- 95.** McClure RS, Athanasopoulos LV, McGurk S, Davidson MJ, Couper GS, Cohn LH. One thousand minimally invasive mitral valve operations: early outcomes, late outcomes, and echocardiographic follow-up. *J Thorac Cardiovasc Surg.* 2013;145:1199-206.
- 96.** Rozich JD, Carabello BA, Usher BW, Kratz JM, Bell AE, Zile MR. Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation. Mechanisms for differences in postoperative ejection performance. *Circulation.* 1992;86:1718-26.
- 97.** Rushmer RF. Initial phase of ventricular systole: asynchronous contraction. *Am J Physiol.* 1956;184:188-94.
- 98.** Sarris GE, Cahill PD, Hansen DE, Derby GC, Miller DC. Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of valvular-ventricular interaction. *J Thorac Cardiovasc Surg.* 1988;95:969-79.
- 99.** 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.
- 100.** 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;94:1870-9.
- 101.** Bolling SF, Li S, O'Brien SM, Brennan JM, Prager RL, Gammie JS. Predictors of mitral valve repair: clinical and surgeon factors. *Ann Thorac Surg.* 2010;90:1904-11; discussion 12.
- 102.** Chauvaud S, Fuzellier JF, Berrebi A, Deloche A, Fabiani JN, Carpentier A. Long-term (29 years) results of reconstructive surgery in rheumatic mitral valve insufficiency. *Circulation.* 2001;104:112-5.
- 103.** 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.
- 104.** Grossi EA, Galloway AC, Miller JS, et al. Valve repair versus replacement for mitral insufficiency: when is a mechanical valve still indicated? *J Thorac Cardiovasc Surg.* 1998;115:389-96.
- 105.** Gillinov AM, Blackstone EH, Cosgrove DM III, et al. Mitral valve repair with aortic valve replacement is superior to double valve replacement. *J Thorac Cardiovasc Surg.* 2003;125:1372-87.
- 106.** Suri RM, Vanoverschelde JL, 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.
- 107.** Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation.* 2006;113:2238-44.
- 108.** Gillinov AM, Blackstone EH, Nowicki ER, et al. Valve repair versus valve replacement for degenerative mitral valve disease. *J Thorac Cardiovasc Surg.* 2008;135:885-93, 93.e1-2.
- 109.** Duran CM, Gometza B, Saad E. Valve repair in rheumatic mitral disease: an unsolved problem. *J Card Surg.* 1994;9:282-5.
- 110.** Suri RM, Schaff HV, Dearani JA, et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. *J Thorac Cardiovasc Surg.* 2009;137:1071-6.
- 111.** Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation.* 2009;119:797-804.
- 112.** 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.
- 113.** Enriquez-Sarano M, Suri RM, Clavel MA, 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.
- 114.** 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.
- 115.** Suri RM, Schaff HV, Dearani JA, et al. Determinants of early decline in ejection fraction after surgical correction of mitral regurgitation. *J Thorac Cardiovasc Surg.* 2008;136:442-7.
- 116.** Naji P, Griffin BP, Barr T, et al. Importance of exercise capacity in predicting outcomes and determining optimal timing of surgery in significant primary mitral regurgitation. *J Am Heart Assoc.* 2014;3:e001010.
- 117.** Cox JL. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J Thorac Cardiovasc Surg.* 1991;101:584-92.
- 118.** 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.
- 119.** Kawaguchi AT, Kosakai Y, Sasako Y, Eishi K, Nakano K, Kawashima Y. Risks and benefits of combined maze procedure for atrial fibrillation associated with organic heart disease. *J Am Coll Cardiol.* 1996;28:985-90.
- 120.** Kobayashi J, Kosakai Y, Isobe F, et al. Rationale of the Cox Maze procedure for atrial fibrillation during redo mitral valve operations. *J Thorac Cardiovasc Surg.* 1996;112:1216-21; discussion 22.

- 121.** Ngaage DL, Schaff HV, Mullany CJ, et al. Influence of preoperative atrial fibrillation on late results of mitral repair: is concomitant ablation justified? *Ann Thorac Surg.* 2007;84:434-42; discussion 42-43.
- 122.** Olasinska-Wisniewska A, Mularek-Kubzdela T, Grajek S, et al. Impact of atrial remodeling on heart rhythm after radiofrequency ablation and mitral valve operations. *Ann Thorac Surg.* 2012;93:1449-55.
- 123.** Raine D, Dark J, Bourke JP. Effect of mitral valve repair/replacement surgery on atrial arrhythmia behavior. *J Heart Valve Dis.* 2004;13:615-21.
- 124.** Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med.* 2011;364:1395-406.
- 125.** 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.
- 126.** Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol.* 2012;59:130-9.
- 127.** Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. 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.
- 128.** Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. *J Am Coll Cardiol.* 2015;65:1231-48.
- 129.** Obadia JF, Armoiry X, Lung B, et al. The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation. *EuroIntervention.* 2015;10:1354-60.
- 130.** Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation.* 2001;103:1759-64.
- 131.** 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.
- 132.** Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. 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.
- 133.** 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.
- 134.** Mihaljevic T, Lam BK, 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.
- 135.** Harris KM, Sundt TM III, Aeppli D, Sharma R, Barzilai B. Can late survival of patients with moderate ischemic mitral regurgitation be impacted by intervention on the valve? *Ann Thorac Surg.* 2002;74:1468-75.
- 136.** 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.
- 137.** 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.
- 138.** 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.
- 139.** 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.
- 140.** 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.* 2013;64:182-92.
- 141.** 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; 6e1-5.
- 142.** Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. *Eur Heart J.* 2016;37:2658-67.
- 143.** Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. *JAMA.* 2015;313:1435-42.
- 144.** McClure RS, McGurk S, Vecasco 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.
- 145.** Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA.* 2014;312:1323-9.
- 146.** Repack A, Ziganshin BA, Elefteriades JA, Mukherjee SK. Comparison of quality of life perceived by patients with bioprosthetic versus mechanical valves after composite aortic root replacement. *Cardiology.* 2016;133:3-9.
- 147.** 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.
- 148.** Rahimtoola SH. Choice of prosthetic heart valve in adults: an update. *J Am Coll Cardiol.* 2010;55:2413-26.
- 149.** 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.
- 150.** Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards Perimount valve in aortic position. *Ann Thorac Surg.* 2015;99:831-7.
- 151.** Bourguignon T, Bouquiaux-Stablo AL, 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.
- 152.** Ye J, Cheung A, Yamashita M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an eight-year single-center experience. *J Am Coll Cardiol Intv.* 2015;8:1735-44.
- 153.** 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.
- 154.** Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA.* 2014;312:162-70.
- 155.** Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. 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.
- 156.** 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.
- 157.** 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.
- 158.** Badhwar V, Ofenloch JC, Rovin JD, van Gelder HM, Jacobs JP. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg.* 2012;93:748-53.
- 159.** 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; discussion 84.
- 160.** Kulik A, Bédard P, Lam BK, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. *Eur J Cardiothorac Surg.* 2006;30:485-91.
- 161.** 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.
- 162.** McClure RS, Narayanasamy N, Wiegerinck E, et al. Late outcomes for aortic valve replacement with the Carpentier-Edwards pericardial bioprosthesis: up to 17-year follow-up in 1,000 patients. *Ann Thorac Surg.* 2010;89:1410-6.
- 163.** Banbury MK, Cosgrove DM III, Thomas JD, et al. Hemodynamic stability during 17 years of the

Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg.* 2002;73:1460-5.

**164.** Borger MA, Ivanov J, Armstrong S, Christie-Hrybinsky D, Feindel CM, David TE. Twenty-year results of the Hancock II bioprosthesis. *J Heart Valve Dis.* 2006;15:49-55; discussion -6.

**165.** Dellgren G, David TE, Raanani E, Armstrong S, Ivanov J, Rakowski H. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc Surg.* 2002;124:146-54.

**166.** Mykén PS, Bech-Hansen O. A 20-year experience of 1712 patients with the Biorcor porcine bioprosthesis. *J Thorac Cardiovasc Surg.* 2009;137:76-81.

**167.** Charitos EI, Takkenberg JJM, Hanke T, et al. Reoperations on the pulmonary autograft and pulmonary homograft after the Ross procedure: an update on the German Dutch Ross Registry. *J Thorac Cardiovasc Surg.* 2012;144:813-21; discussion 21-23.

**168.** El-Hamamsy I, Eryigit Z, Stevens LM, 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.

**169.** Mokhles MM, Rizopoulos D, Andrinopoulou ER, et al. Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. *Eur Heart J.* 2012;33:2213-24.

**170.** Edmunds LH Jr. Thrombotic and bleeding complications of prosthetic heart valves. *Ann Thorac Surg.* 1987;44:430-45.

**171.** Tiede DJ, Nishimura RA, Gastineau DA, Mullany CJ, Orszulak TA, Schaff HV. Modern management of prosthetic valve anticoagulation. *Mayo Clin Proc.* 1998;73:665-80.

**172.** Aziz F, Corder M, Wolffe J, Comerota AJ. Anticoagulation monitoring by an anticoagulation service is more cost-effective than routine physician care. *J Vasc Surg.* 2011;54:1404-7.

**173.** Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med.* 1998;158:1641-7.

**174.** Wittkowsky AK, Nutescu EA, Blackburn J, et al. Outcomes of oral anticoagulant therapy managed by telephone vs in-office visits in an anticoagulation clinic setting. *Chest.* 2006;130:1385-9.

**175.** Lalonde L, Martineau J, Blais N, et al. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. *Am Heart J.* 2008;156:148-54.

**176.** Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest.* 2005;127:1515-22.

**177.** Locke C, Ravnan SL, Patel R, Uchizono JA. Reduction in warfarin adverse events requiring patient hospitalization after implementation of a pharmacist-managed anticoagulation service. *Pharmacotherapy.* 2005;25:685-9.

**178.** Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. 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:e5765-600.

**179.** Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation.* 1994;89:635-41.

**180.** Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med.* 1995;333:11-7.

**181.** Schlitt A, von Bardeleben RS, Ehrlich A, et al. Clopidogrel and aspirin in the prevention of thromboembolic complications after mechanical aortic valve replacement (CAPTA). *Thromb Res.* 2003;109:131-5.

**182.** Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest.* 2001;119:2205-75.

**183.** Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet.* 2009;374:565-76.

**184.** Acar J, lung 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.

**185.** 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.

**186.** Torella M, Torella D, Chiodini P, et al. LOWERing the Intensity of oral anticoGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. *Am Heart J.* 2010;160:171-8.

**187.** Horstkotte D, Scharf RE, Schultheiss HP. Intracardiac thrombosis: patient-related and device-related factors. *J Heart Valve Dis.* 1995;4:114-20.

**188.** Pruefer D, Dahm M, Dohmen G, Horstkotte D, Bergemann R, Oelert H. 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 Suppl Q:Q39-43.

**189.** Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg.* 1997;113:910-6.

**190.** Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med.* 1993;329:524-9.

**191.** Aramendi JJ, Mestres CA, Campos V, Martinez-Leon J, Munoz G, Navas C. 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.

**192.** Colli A, Mestres CA, Castella M, Gherli T. 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.

**193.** 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.

**194.** Nuñez L, Gil Aguado M, Larrea JL, Celemin D, Oliver J. Prevention of thromboembolism using aspirin after mitral valve replacement with porcine bioprosthesis. *Ann Thorac Surg.* 1984;37:84-7.

**195.** Brennan JM, Edwards FH, Zhao Y, et al. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *J Am Coll Cardiol.* 2012;60:971-7.

**196.** Egbe AC, Pislaru SV, Pellikka PA, et al. Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol.* 2015;66:2285-94.

**197.** 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.

**198.** Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-51.

**199.** Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med.* 2015;373:823-33.

**200.** 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.

**201.** Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093-104.

**202.** Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-92.

**203.** Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med.* 2015;373:2015-24.

**204.** Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883-91.

**205.** 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.

**206.** Russo A, Grigioni F, Avierinos JF, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J Am Coll Cardiol.* 2008;51:1203-11.

**207.** ElBardissi AW, DiBardino DJ, Chen FY, Yamashita MH, Cohn LH. Is early antithrombotic therapy necessary in patients with bioprosthetic aortic valves in normal sinus rhythm? *J Thorac Cardiovasc Surg.* 2010;139:1137-45.

**208.** Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68:1082-115.

**209.** 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; discussion 10-11.

**210.** Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol.* 2016;68:2059-69.

**211.** Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J.* 2016;37:2263-71.

**212.** FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. December 19, 2012. 2012.

**213.** 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 (RE-ALIGN). *Am Heart J.* 2012;163:931-7.e1.

**214.** 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. Erratum. *Chest.* 2012;141:e326S-350.

**215.** 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 (LIWACAP). *Clin Appl Thromb Hemost.* 2007;13:241-8.

**216.** Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quinones MA, Zoghbi WA. 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.

**217.** 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.

**218.** 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.

**219.** Montorsi P, De Bernardi F, Muratori M, Cavoretto D, Pepi M. Role of cine-fluoroscopy, transthoracic, and transesophageal echocardiography in patients with suspected prosthetic heart valve thrombosis. *Am J Cardiol.* 2000;85:58-64.

**220.** 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.

**221.** 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.

**222.** Symersky P, Budde RPJ, de Mol BAJM, Prokop M. 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.

**223.** Gürsoy OM, Karakoyun S, Kalçık M, Ozkan M. The incremental value of RT three-dimensional TEE in the evaluation of prosthetic mitral valve ring thrombosis complicated with thromboembolism. *Echocardiography.* 2013;30:E198-201.

**224.** Tong AT, Roudaut R, Özkan 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.

**225.** Keuleers S, Herijgers P, Herregods MC, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. *Am J Cardiol.* 2011;107:275-9.

**226.** Roudaut R, Lafitte S, Roudaut MF, 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.

**227.** Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. *Circulation.* 2009;120:1108-14.

**228.** Cáceres-Lóriga FM, Pérez-López H, Morlans-Hernandez 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.

**229.** Özkan M, Gündüz S, Biteker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *J Am Coll Cardiol Img.* 2013;6:206-16.

**230.** 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.

**231.** 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.

**232.** Deviri E, Sareli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. *J Am Coll Cardiol.* 1991;17:646-50.

**233.** Karthikeyan G, Senguttuvan NB, Joseph J, Devasenapathy N, Bahl VK, Airan B. 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.

**234.** Huang G, Schaff HV, Sundt TM, Rahimtoola SH. Treatment of obstructive thrombosed prosthetic heart valve. *J Am Coll Cardiol.* 2013;62:1731-6.

**235.** Özkan M, Gündüz S, Gürsoy OM, et al. Ultrasound 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.

**236.** Laschinger JC, Wu C, Ibrahim NG, Shuren JE. Reduced leaflet motion in bioprosthetic aortic valves—the FDA perspective. *N Engl J Med.* 2015;373:1996-8.

**237.** Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation.* 2009;119:1034-48.

**238.** 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.

**239.** Maganti M, Rao V, Armstrong S, Feindel CM, Scully HE, David TE. Redo valvular surgery in elderly patients. *Ann Thorac Surg.* 2009;87:521-5.

**240.** Leontyev S, Borger MA, Davierwala P, et al. Redo aortic valve surgery: early and late outcomes. *Ann Thorac Surg.* 2011;91:1120-6.

**241.** 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; discussion 304.

**242.** Jander N, Kienzle RP, Kayser G, Neumann FJ, Gohlke-Baerwolf C, Minners J. Usefulness of phenprocoumon for the treatment of obstructing thrombus in bioprostheses in the aortic valve position. *Am J Cardiol.* 2012;109:257-62.

**243.** Butnaru A, Shaheen J, Tzivoni D, Tauber R, Bitran D, Silberman S. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. *Am J Cardiol.* 2013;112:1439-44.

**244.** 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.

**245.** De Marchena E, Mesa J, Pomenti S, et al. Thrombus formation following transcatheter aortic valve replacement. *J Am Coll Cardiol Intv.* 2015;8:728-39.

**246.** Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv.* 2015;8.

**247.** Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation.* 2010;121:1848-57.

**248.** Phan K, Zhao DF, Wang N, Huo YR, Di EM, Yan TD. Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. *J Thorac Dis.* 2016;8:E83-93.

**249.** Administration USFaD. FDA expands use of CoreValue System for aortic "valve-in-valve replacement". March 30, 2015. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440535.htm>. Accessed January 20, 2017.

**250.** Akins CW, Bitondo JM, Hilgenberg AD, Vlahakes GJ, Madsen JC, MacGillivray TE. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. *J Heart Valve Dis.* 2005;14:792-9; discussion 9-800.

**251.** Miller DL, Morris JJ, Schaff HV, Mullany CJ, Nishimura RA, Orszulak TA. Reoperation for aortic valve periprosthetic leakage: identification of patients at risk and results of operation. *J Heart Valve Dis.* 1995;4:160-5.

**252.** 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.

- 253.** Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. *Circ Cardiovasc Interv.* 2011;4:314-21.
- 254.** Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. *J Am Coll Cardiol.* 2011;58:2218-24.
- 255.** 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.
- 256.** Gordon SM, Serkey JM, Longworth DL, Lytle BW, Cosgrove DM III. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience 1992-1997. *Ann Thorac Surg.* 2000;69:1388-92.
- 257.** Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *JAMA.* 2003;289:1933-40.
- 258.** 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.
- 259.** 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.
- 260.** Tornos P, Sanz E, Permanyer-Miralda G, Almirante B, Planes AM, Soler-Soler J. Late prosthetic valve endocarditis. Immediate and long-term prognosis. *Chest.* 1992;101:37-41.
- 261.** Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA.* 2007;297:1354-61.
- 262.** 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.
- 263.** 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.
- 264.** Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965-1995. *Clin Infect Dis.* 2001;32:50-62.
- 265.** Hill EE, Herijgers P, Claus P, Vanderschueren S, Herregods MC, Peetermans WE. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. *Eur Heart J.* 2007;28:196-203.
- 266.** Melgar GR, Nasser RM, Gordon SM, Lytle BW, Keys TF, Longworth DL. Fungal prosthetic valve endocarditis in 16 patients. An 11-year experience in a tertiary care hospital. *Medicine (Baltimore).* 1997;76:94-103.
- 267.** Remadi JP, Habib G, Nadji G, et al. Predictors of death and impact of surgery in *Staphylococcus aureus* infective endocarditis. *Ann Thorac Surg.* 2007;83:1295-302.
- 268.** Wolff M, Witchitz S, Chastang C, Regnier B, Vachon F. 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.
- 269.** Anguera I, Miro JM, Vilacosta I, et al. Aorticavitary 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.
- 270.** Chan KL. Early clinical course and long-term outcome of patients with infective endocarditis complicated by perivalvular abscess. *CMAJ.* 2002;167:19-24.
- 271.** 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.
- 272.** 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.
- 273.** Wang K, Gobel F, Gleason DF, Edwards JE. Complete heart block complicating bacterial endocarditis. *Circulation.* 1972;46:939-47.
- 274.** Hill EE, Herijgers P, Claus P, Vanderschueren S, Peetermans WE, Herregods MC. Abscess in infective endocarditis: the value of transesophageal echocardiography and outcome: a 5-year study. *Am Heart J.* 2007;154:923-8.
- 275.** 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.
- 276.** 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.
- 277.** Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA.* 2012;307:1727-35.
- 278.** Ho HH, Siu CW, Yiu KH, Tse HF, Chui WH, Chow WH. Prosthetic valve endocarditis in a multi-center registry of Chinese patients. *Asian Cardiovasc Thorac Ann.* 2010;18:430-4.
- 279.** Rundström H, Kennergren C, Andersson R, Alestig K, Hogevik H. Pacemaker endocarditis during 18 years in Göteborg. *Scand J Infect Dis.* 2004;36:674-9.
- 280.** Sohail MR, Uslan DZ, Khan AH, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc.* 2008;83:46-53.
- 281.** Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med.* 2012;366:2466-73.
- 282.** Mügge A, Daniel WG, Frank G, Lichtlen PR. 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.
- 283.** 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.
- 284.** Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. *J Thorac Cardiovasc Surg.* 1995;110:1745-55.
- 285.** Barsic B, Dickerman S, Krajcinovic V, et al. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. *Clin Infect Dis.* 2013;56:209-17.
- 286.** García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation.* 2013;127:2272-84.

---

**KEY WORDS** ACC/AHA Clinical Practice Guidelines Focused Update, anticoagulation therapy, aortic stenosis, cardiac surgery, heart valves, mitral regurgitation, prosthetic valves, transcatheter aortic valve replacement, tricuspid stenosis, valvular heart disease

**APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2017 AHA/ACC FOCUSED UPDATE OF THE 2014 AHA/ACC GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (JANUARY 2016)**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Rick A. Nishimura (Co-Chair)	Mayo Clinic, Division of Cardiovascular Disease—Judd and Mary Morris Leighton Professor of Medicine	None	None	None	None	None	None	None
Catherine M. Otto (Co-Chair)	University of Washington Division of Cardiology—Professor of Medicine	None	None	None	None	None	None	None
Robert O. Bonow	Northwestern University Feinberg School of Medicine—Goldberg Distinguished Professor of Cardiology	None	None	None	None	None	None	None
Blase A. Carabello	East Carolina University, Brody School of Medicine, East Carolina Heart Institute—Chief Cardiology Director	None	None	None	■ Edwards Lifesciences (DSMB)†	■ Medtronic†	None	3.2.4, 7.3.3, 7.4.3, and 11.1.
John P. Erwin III	Texas A&M College of Medicine, Baylor Scott and White Health—Senior Staff Cardiologist, Clinical Professor and Chair of Internal Medicine	None	None	None	None	None	None	None
Lee A. Fleisher	University of Pennsylvania, Department of Anesthesiology—Professor of Anesthesiology	None	None	None	None	None	None	None
Hani Jneid	Baylor College of Medicine—Associate Professor of Medicine, Director of Interventional Cardiology Research; The Michael E. DeBakey VA Medical Center—Director of Interventional Cardiology	None	None	None	None	None	None	None
Michael J. Mack	The Heart Hospital Baylor Plano—Director	None	None	None	None	■ Abbott Vascular ■ Edwards Lifesciences	None	3.2.4, 7.3.3, 7.4.3, and 11.1.
Christopher J. McLeod	Mayo Clinic, Division of Cardiovascular Disease—Assistant Professor of Medicine	None	None	None	None	None	None	None
Patrick T. O’Gara	Brigham and Women’s Hospital—Professor of Medicine; Harvard Medical School—Director of Clinical Cardiology	None	None	None	None	None	None	None
Vera H. Rigolin	Northwestern University Feinberg School of Medicine—Professor of Medicine; Northwestern Memorial Hospital—Medical Director, Echocardiography Laboratory	None	None	None	■ Pfizer	None	None	None
Thoralf M. Sundt III	Massachusetts General Hospital—Chief, Division of Cardiac Surgery, Harvard Medical School—Professor of Surgery	None	None	None	■ Edwards LifeSciences—Partner trial (PI) ■ Medtronic—Perigon trial (PI)	■ Thrasos (Steering Committee)‡	None	3.2.4, 7.3.3, 7.4.3, and 11.1.
Annamarie Thompson	Duke University Medical Center—Department of Anesthesiology, Professor of Anesthesiology; Residency Program Director	None	None	None	None	None	None	None

This table represents 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 ≥\$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC/AHA, a person has a *relevant relationship* IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the document or makes a competing drug or device addressed in the document; or c) the *person or a member of the person’s household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.

†No financial benefit.

‡Significant relationship.

ACC indicates American College of Cardiology; AHA, American Heart Association; Partner, Placement of Aortic Transcatheter Valve; Perigon, Pericardial Surgical Aortic Valve Replacement; and VA, Veterans Affairs.



**APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2017 AHA/ACC FOCUSED UPDATE OF THE 2014 AHA/ACC GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (SEPTEMBER 2016)**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Salvatore P. Costa	Official Reviewer—AHA	Dartmouth-Hitchcock Medical Center; Section of Cardiology	None	None	None	None	None	None
Federico Gentile	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines Lead Reviewer	Centro Medico Diagnostico—Director, Cardiovascular Disease	None	None	None	None	None	None
Lawrence G. Rudski	Official Reviewer—ACC Board of Governors	Jewish General Hospital, McGill University—Professor of Medicine; Integrated Cardiovascular Sciences Program—Director	None	None	■ Medtronic*	■ Sanofi/ Genzyme*	■ GE Healthcare* ■ CSE†	None
John J. Ryan	Official Reviewer—AHA	University of Utah Health Sciences Center—Division of Cardiovascular Medicine	None	None	None	None	■ Novartis	None
David Adams	Organizational Reviewer—AATS	Mount Sinai Medical Center; Department of Cardiovascular Surgery—Professor and System Chair	None	None	None	■ Medtronic ■ NeoChord	■ Edwards Lifesciences* ■ Medtronic*	None
Joseph E. Bavaria	Organizational Reviewer—STS	Hospital of the University of Pennsylvania; Division of Cardiovascular Surgery—Vice Chief; Thoracic Aortic Surgery Program—Director; Transcatheter Valve Program—Co-Director	None	None	None	■ CytoSorbents ■ Edwards Lifesciences ■ Medtronic ■ St. Jude Medical ■ Vascutek ■ W.L. Gore	■ Edwards Lifesciences ■ Medtronic	None
Wael A. Jaber	Organizational Reviewer—ASE	Cleveland Clinic Foundation, Cardiovascular Medicine, Cardiovascular Imaging Core Laboratory—Director	None	None	None	■ Edwards Lifesciences	None	None
Stanton Sherman	Organizational Reviewer—SCA	Brigham and Women's Hospital, Cardiac Anesthesia Division—Director; Harvard Medical School—Professor	None	None	None	None	■ Philips Healthcare ■ National Board of Echocardiography†	None
Molly Szerlip	Organizational Reviewer—SCAI	The Heart Group—Interventional Cardiologist; The Heart Hospital Baylor Plano—Medical Director, Inpatient and Outpatient Valve Program	■ Edwards Lifesciences ■ Medtronic	■ Abiomed† ■ Edwards Lifesciences†	None	None	■ Edwards Lifesciences ■ Medtronic	None
Kim K. Birtcher	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston College of Pharmacy—Clinical Professor	■ Jones & Bartlett Learning	None	None	None	None	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Vera Bittner	Content Reviewer—ACC Prevention of Cardiovascular Disease Section Leadership Council	University of Alabama at Birmingham—Professor of Medicine; Section Head, General Cardiology, Prevention and Imaging	<ul style="list-style-type: none"> <li>■ Eli Lilly</li> <li>■ ABIM*</li> <li>■ Alabama ACC</li> <li>■ Alabama ACP</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Amgen</li> <li>■ AstraZeneca*</li> <li>■ Bayer Healthcare*</li> <li>■ DalCor*</li> <li>■ Pfizer</li> <li>■ Sanofi-aventis*</li> </ul>	<ul style="list-style-type: none"> <li>■ National Lipid Association</li> </ul>	None
Emmanouil Brilakis	Content Reviewer	Laboratory, VA North Texas Healthcare System—Director Cardiac Catheterization	<ul style="list-style-type: none"> <li>■ Abbott Vascular*</li> <li>■ Asahi</li> <li>■ Cardinal Health</li> <li>■ Elsevier</li> <li>■ GE Healthcare</li> <li>■ St. Jude Medical</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Boston Scientific*</li> <li>■ InfraRedx*</li> </ul>	<ul style="list-style-type: none"> <li>■ Abbott Vascular†</li> <li>■ AstraZeneca†</li> <li>■ Cerenis Therapeutics*</li> <li>■ Cordis*</li> <li>■ Daiichi Sankyo*</li> <li>■ Guerbet*</li> <li>■ InfraRedx*</li> <li>■ SCAI</li> </ul>	None
James Fang	Content Reviewer	University of Utah School of Medicine—Chief of Cardiovascular Medicine; University of Utah Health Care—Director, Cardiovascular Service Line	<ul style="list-style-type: none"> <li>■ Accordia</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Actelion (DSMB)</li> <li>■ Cardiocell (DSMB)</li> <li>■ NIH (DSMB)</li> </ul>	<ul style="list-style-type: none"> <li>■ CardioKinetix</li> <li>■ NIH</li> <li>■ Novartis</li> </ul>	None
Michael S. Firstenberg	Content Reviewer—ACC Surgeons' Council	The Summa Health System—Thoracic and Cardiac Surgery	<ul style="list-style-type: none"> <li>■ Allmed*</li> <li>■ Johnson &amp; Johnson</li> <li>■ Maquet Cardiovascular*</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Grisfols</li> </ul>	None
Annetine Gelijns	Content Reviewer	Mount Sinai Medical Center, Population Health Science and Policy—Professor and System Chair	None	None	None	None	<ul style="list-style-type: none"> <li>■ Icahn School of Medicine at Mount Sinai*</li> <li>■ NIH</li> </ul>	None
Samuel Gidding	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Nemours/Alfred I. duPont Hospital for Children—Chief, Division of Pediatric Cardiology	<ul style="list-style-type: none"> <li>■ FH Foundation†</li> <li>■ International FH Foundation†</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ FH Foundation†</li> <li>■ NIH*</li> </ul>	None	None
Paul A. Grayburn	Content Reviewer	Baylor Heart and Vascular Institute—Director of Cardiology Research	<ul style="list-style-type: none"> <li>■ Abbott Vascular*</li> <li>■ Tendyne</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Abbott Vascular†</li> <li>■ Boston Scientific†</li> <li>■ Medtronic†</li> <li>■ Tendyne†</li> <li>■ Valtech Cardio†</li> </ul>	<ul style="list-style-type: none"> <li>■ American Journal of Cardiology</li> <li>■ NeoChord†</li> </ul>	None
Richard Grimm	Content Reviewer—ACC Heart Failure and Transplant Section Leadership Council	Cleveland Clinic Foundation, Department of Cardiovascular Medicine—Medical Director of Echo Lab	<ul style="list-style-type: none"> <li>■ Abbott Laboratories</li> </ul>	None	None	None	None	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jonathan L. Halperin	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Mount Sinai Medical Center—Professor of Medicine	<ul style="list-style-type: none"> <li>■ AstraZeneca</li> <li>■ Bayer</li> <li>■ Boston Scientific</li> </ul>	None	None	None	None	None
Alex Iribarne	Content Reviewer—ACC Surgeons' Council	Dartmouth Hitchcock Medical Center—Attending Cardiac Surgeon; Cardiac Surgical Research—Director; The Dartmouth Institute—Assistant Professor of Surgery	None	None	None	None	None	None
Craig January	Content Reviewer	University of Wisconsin-Madison—Professor of Medicine, Cardiovascular Medicine Division	None	None	None	None	None	None
José Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center—Associate Professor of Internal Medicine	None	None	None	None	<ul style="list-style-type: none"> <li>■ Medtronic*</li> <li>■ St. Jude Medical*</li> </ul>	None
Kyle W. Klarich	Content Reviewer	Mayo Clinic—Professor of Medicine	None	None	None	None	None	None
Gautam Kumar	Content Reviewer—ACC Interventional Section Leadership Council	Emory University, Division of Cardiology—Assistant Professor of Medicine	<ul style="list-style-type: none"> <li>■ Abiomed</li> <li>■ CSI Medical</li> <li>■ T3 Labs</li> <li>■ Trireme Medical</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Orbus-Neich Medical</li> <li>■ Osprey Medical</li> <li>■ Stentys</li> </ul>	None
Richard Lange	Content Reviewer	Texas Tech University Health Sciences Center at El Paso—President	None	None	None	None	None	None
Susan T. Laing	Content Reviewer—ACC Heart Failure and Transplant Section Leadership Council	UT Health Science Center at Houston (UT Health)—Professor of Medicine, Division of Cardiology, Associate Chief; Director of Echocardiography	None	None	None	None	None	None
Glenn Levine	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit	None	None	None	None	None	<ul style="list-style-type: none"> <li>■ Defendant, Hospital Death, 2016</li> <li>■ Defendant, Catheterization Laboratory Procedure, 2016</li> </ul>
Brian Lindman	Content Reviewer	Washington University School of Medicine in St. Louis, Cardiovascular Division—Associate Professor of Medicine	<ul style="list-style-type: none"> <li>■ Roche Diagnostics</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ AHA Clinical Research Grant*</li> <li>■ Barnes-Jewish Hospital Foundation*</li> <li>■ Doris Duke Charitable Foundation*</li> <li>■ Edwards Lifesciences*</li> <li>■ NIH</li> <li>■ Roche Diagnostics*</li> </ul>	<ul style="list-style-type: none"> <li>■ NIH*</li> </ul>	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
D. Craig Miller	Content Reviewer	Stanford University Medical Center—Cardiothoracic Surgeon	<ul style="list-style-type: none"> <li>■ Medtronic</li> <li>■ NHLBI</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Abbott Laboratories</li> <li>■ Edwards Lifesciences</li> <li>■ Medtronic</li> </ul>	None	None
Stefano Nistri	Content Reviewer	CMSR Veneto Medica—Chief, Cardiology Service	None	None	None	None	None	None
Philippe Pibarot	Content Reviewer	Université Laval—Professor of Medicine; Canada Research in Valvular Heart Diseases—Chair	None	None	None	<ul style="list-style-type: none"> <li>■ Cardiac Phoenix*</li> <li>■ Edwards Lifesciences*</li> <li>■ Medtronic*</li> <li>■ V-Wave*</li> <li>■ Canadian Institute of Health</li> </ul>	None	None
Hartzell V. Schaff	Content Reviewer	Mayo Clinic—Professor of Surgery	None	None	None	None	None	None
Allan Schwartz	Content Reviewer	Columbia University Medical Center—Chief, Division of Cardiology, Vice Chair of Department of Medicine	None	None	None	None	None	None
Karen Stout	Content Reviewer	University of Washington—Director, Adult Congenital Heart Disease Program, Professor, Internal Medicine and Pediatrics	None	None	None	None	None	None
Rakesh Suri	Content Reviewer	Cleveland Clinic Foundation—Professor of Surgery, Department of Thoracic and Cardiovascular Surgery	<ul style="list-style-type: none"> <li>■ Sorin†</li> <li>■ Abbott</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ St. Jude Medical</li> </ul>	<ul style="list-style-type: none"> <li>■ St. Jude Medical</li> </ul>	None
Vinod Thourani	Content Reviewer	Emory University School of Medicine, Division of Cardiothoracic Surgery—Professor of Surgery; Structural Heart and Valve Center of the Emory Heart and Vascular Center—Co-Director; Emory University Hospital Midtown—Chief of Cardiothoracic Surgery	<ul style="list-style-type: none"> <li>■ Edwards Lifesciences</li> <li>■ St. Jude Medical</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Abbott Medical</li> <li>■ Boston Scientific†</li> <li>■ Edwards Lifesciences†</li> <li>■ Medtronic†</li> </ul>	None	None
E. Murat Tuzcu	Content Reviewer	Cleveland Clinic Abu Dhabi—Cardiovascular Medicine	None	None	None	None	<ul style="list-style-type: none"> <li>■ Boston Scientific</li> <li>■ Direct Flow Medical</li> <li>■ St. Jude Medical</li> <li>■ Tendyne</li> </ul>	None

Continued on the next page

## APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Andrew Wang	Content Reviewer	Duke University Medical Center—Professor of Medicine; Cardiovascular Disease Fellowship Program—Director	<ul style="list-style-type: none"> <li>■ Heart Metabolics*</li> <li>■ ACP*</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Abbott Vascular*</li> <li>■ Gilead Sciences*</li> <li>■ Maokardia*</li> <li>■ Edwards Lifesciences</li> <li>■ Medtronic</li> </ul>	None
L. Samuel Wann	Content Reviewer	Columbia St. Mary's Cardiovascular Physicians—Clinical Cardiologist	<ul style="list-style-type: none"> <li>■ United Healthcare</li> </ul>	None	None	None	None	None
Frederick Welt	Content Reviewer—ACC Interventional Section Leadership Council	University of Utah Health Sciences Center, Division of Cardiology—Director, Interventional Cardiology	<ul style="list-style-type: none"> <li>■ Medtronic</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Athersys</li> <li>■ Capricor</li> <li>■ CardioKinetix</li> <li>■ Medtronic</li> <li>■ Renova Therapeutics</li> <li>■ Siemens</li> <li>■ Teva Pharmaceuticals</li> <li>■ Washington University</li> </ul>	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. 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  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5,000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to <http://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.

\*Significant relationship.

†No financial benefit.

AAFP indicates American Academy of Family Physicians; AATS, American Association for Thoracic Surgery; ABIM, American Board of Internal Medicine; ACC, American College of Cardiology; ACP, American College of Physicians; AHA, American Heart Association; ASE, American Society of Echocardiography; CSE, Canadian Society of Echocardiography; DSMB, data safety monitoring board; FH, familial hyperlipidemia; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; SCAI, Society for Cardiovascular Angiography and Interventions; SCA, Society of Cardiovascular Anesthesiologists; STS, Society of Thoracic Surgeons; UT, University of Texas; and WVU, West Virginia University.

### APPENDIX 3. ABBREVIATIONS

---

AF = atrial fibrillation

AS = aortic stenosis

AVR = aortic valve replacement

CABG = coronary artery bypass graft surgery

CI = confidence interval

CT = computed tomography

DOACs = direct oral anticoagulants

EF = ejection fraction

GDMT = guideline-directed management and therapy

HF = heart failure

HR = hazard ratio

IE = infective endocarditis

INR = International Normalized Ratio

LV = left ventricular

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

MR = mitral regurgitation

MS = mitral stenosis

MVR = mitral valve replacement

NYHA = New York Heart Association

RCT = randomized controlled trial

TAVR = transcatheter aortic valve replacement

VHD = valvular heart disease

VKA = vitamin K antagonist

---