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

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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 online Comprehensive RWI Data Supplement table is available with this article at http://circ.ahajournals.org/lookup/suppl;doi:10.1161/CIR.0000000000000503/-/DC1.

The online Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl;doi:10.1161/CIR.0000000000000503/-/DC2.


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

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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 at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy. 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000503/-/DC1). Comprehensive disclosure information for the Task Force is available at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces.

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

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

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; EG, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000503/-/DC2).

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).

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.
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.

### Recommendation for IE Prophylaxis

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
</table>
| IIa | C-LD | 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):  
1. Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts.  
2. Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords.  
3. Previous IE.  
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.  
5. Cardiac transplant with valve regurgitation due to a structurally abnormal valve. | MODIFIED: 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. |

See Online Data Supplements 1 and 2.
2.4.3. Anticoagulation for Atrial Fibrillation in Patients With VHD (New Section)

<p>| Recommendations for Anticoagulation for Atrial Fibrillation (AF) in Patients With VHD |
|----------------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B-NR</td>
<td>Anticoagulation with a vitamin K antagonist (VKA) is indicated for patients with rheumatic mitral stenosis (MS) and AF (34,35).</td>
<td>MODIFIED: 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).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplements 3 and 4.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C-LD</td>
<td>Anticoagulation is indicated in patients with AF and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 2 or greater with native aortic valve disease, tricuspid valve disease, or MR (36-38).</td>
<td>NEW: 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\textsubscript{2}DS\textsubscript{2}-VASc score (35-38).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplements 3 and 4.</td>
<td></td>
</tr>
</tbody>
</table>

A retrospective analysis of administrative claims databases (>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.)

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\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-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\textsubscript{2}DS\textsubscript{2}-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 CHA2DS2-VASc score.

| IIa | 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 CHA2DS2-VASc score of 2 or greater (35-38). |

NEW: 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.

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.
<table>
<thead>
<tr>
<th>Recommendations for Choice of Intervention</th>
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<tbody>
<tr>
<td><strong>COR</strong></td>
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<td>I</td>
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</table>

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.

| 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). | MODIFIED: 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... |
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.

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.

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).

<table>
<thead>
<tr>
<th>IIa</th>
<th>B-R</th>
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</thead>
<tbody>
<tr>
<td><strong>NEW:</strong> New RCT showed noninferiority of TAVR to surgical AVR in symptomatic patients with severe AS at intermediate surgical risk.</td>
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<tr>
<td><strong>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).</strong></td>
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</tr>
<tr>
<td>See Online Data Supplements 5 and 9 (Updated From 2014 VHD Guideline)</td>
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</table>

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 bioprosthesis 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).

<table>
<thead>
<tr>
<th>IIb</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or TAVR for symptomatic patients with severe AS.</td>
<td>2014 recommendation remains current.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III: No Benefit</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (61).</td>
<td>2014 recommendation remains current.</td>
</tr>
</tbody>
</table>
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 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 ≥0.4 cm² and regurgitant volume ≥60 mL), with the understanding that effective regurgitant orifice cutoff of >0.2 cm² is more sensitive and >0.4 cm² 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.
### Table 2. Stages of Secondary MR (Table 16 in the 2014 VHD Guideline)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics*</th>
<th>Associated Cardiac Findings</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| A     | At risk of MR | • Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy | • No MR jet or small central jet area <20% LA on Doppler  
• Small vena contracta <0.30 cm | • Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities  
• Primary myocardial disease with LV dilation and systolic dysfunction | • Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy |
| B     | Progressive MR | • Regional wall motion abnormalities with mild tethering of mitral leaflet  
• Annular dilation with mild loss of central coaptation of the mitral leaflets | • ERO <0.40 cm²†  
• Regurgitant volume <60 mL  
• Regurgitant fraction <50% | • Regional wall motion abnormalities with reduced LV systolic function  
• LV dilation and systolic dysfunction due to primary myocardial disease | • Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy |
| C     | Asymptomatic severe MR | • Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet  
• Annular dilation with severe loss of central coaptation of the mitral leaflets | • ERO ≥0.40 cm²†  
• Regurgitant volume ≥60 mL  
• Regurgitant fraction ≥50% | • Regional wall motion abnormalities with reduced LV systolic function  
• LV dilation and systolic dysfunction due to primary myocardial disease | • Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy |
| D     | Symptomatic severe MR | • Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet  
• Annular dilation with severe loss of central coaptation of the mitral leaflets | • ERO ≥0.40 cm²†  
• Regurgitant volume ≥60 mL  
• Regurgitant fraction ≥50% | • Regional wall motion abnormalities with reduced LV systolic function  
• LV dilation and systolic dysfunction due to primary myocardial disease | • HF symptoms due to MR persist even after revascularization and optimization of medical therapy  
• Decreased exercise tolerance  
• Exertional dyspnea |

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

### 7.3.3. Intervention: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Primary MR Intervention</th>
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<tbody>
<tr>
<td><strong>COR</strong></td>
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<td>I</td>
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<tr>
<td>IIa</td>
</tr>
<tr>
<td>IIa</td>
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</table>
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 >64% and LVESD <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).

<table>
<thead>
<tr>
<th>Level</th>
<th>Class</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>IIa</td>
<td>B</td>
<td>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).</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B) when undergoing cardiac surgery for other indications.</td>
</tr>
<tr>
<td>IIb</td>
<td>C</td>
<td>Mitral valve surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF less than or equal to 30% (stage D).</td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
<td>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).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B</td>
<td>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).</td>
</tr>
</tbody>
</table>

2014 recommendation remains current.
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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C</td>
<td>Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.</td>
<td>2014 recommendation remains current.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>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).</td>
<td>NEW: 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.</td>
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<td>See Online Data Supplement 18. (Updated From 2014 VHD Guideline)</td>
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<td>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).</td>
<td></td>
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<tr>
<td>IIb</td>
<td>B</td>
<td>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).</td>
<td>2014 recommendation remains current.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients with chronic, moderate, ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain (71,72).</td>
<td>MODIFIED: 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.</td>
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<td>See Online Data Supplement 18 (Updated From 2014 VHD Guideline)</td>
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<tr>
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<td>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&lt;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...</td>
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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

<table>
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<tr>
<th>Recommendations for Intervention of Prosthetic Valves</th>
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**MODIFIED:** 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.

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 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
A 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.

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

| IIa | B-NR | 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).  
MODIFIED: LOE updated from B to B-NR. The age limit for mechanical prosthesis was lowered from 60 to 50 years of age. |

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 | 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).  
MODIFIED: 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 |

See Online Data Supplement 20 (Updated From 2014 VHD Guideline)
bleeding, and those undergoing bioprosthetic valve replacement more often require repeat valve surgery.

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).

| 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

<table>
<thead>
<tr>
<th>Favor Mechanical Prosthesis</th>
<th>Favor Bioprosthesis</th>
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</thead>
<tbody>
<tr>
<td>Age &lt;50 y</td>
<td>Age &gt;70 y</td>
</tr>
<tr>
<td>• Increased incidence of structural deterioration with bioprosthesis (15-y risk: 30% for age 40 y, 50% for age 20 y)</td>
<td>• Low incidence of structural deterioration (15-y risk: &lt;10% for age &gt;70 y)</td>
</tr>
<tr>
<td>• Lower risk of anticoagulation complications</td>
<td>• Higher risk of anticoagulation complications</td>
</tr>
<tr>
<td>Patient preference (avoid risk of reintervention)</td>
<td>Patient preference (avoid risk and inconvenience of anticoagulation and absence of valve sounds)</td>
</tr>
<tr>
<td>Low risk of long-term anticoagulation</td>
<td>High risk of long-term anticoagulation</td>
</tr>
<tr>
<td>Compliant patient with either home monitoring or close access to INR monitoring</td>
<td>Limited access to medical care or inability to regulate VKA</td>
</tr>
<tr>
<td>Other indication for long-term anticoagulation (e.g., AF)</td>
<td>Access to surgical centers with low reoperation mortality rate</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Recommendations for Antithrombotic Therapy for Patients with Prosthetic Heart Valves</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
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<td>I</td>
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<td>I</td>
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</tbody>
</table>
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).

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

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).

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

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).

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-R</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td><strong>NEW:</strong> 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.</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-NR</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>NEW:</strong> 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.</td>
</tr>
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</table>

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 | MODIFIED: 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 |
procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR (199,214,215).

change in incidence of thromboembolic events. This may have implications for bridging anticoagulation therapy for patients with prosthetic valves.

“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.

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

<table>
<thead>
<tr>
<th>Recommendation for Mechanical Prosthetic Valve Thrombosis Diagnosis and Follow-Up</th>
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<tbody>
<tr>
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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

### Recommendation for Mechanical Prosthetic Valve Thrombosis Intervention

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B-NR</td>
<td>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).</td>
<td>MODIFIED: 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.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Favor Surgery</th>
<th>Favor Fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readily available surgical expertise</td>
<td>No surgical expertise available</td>
</tr>
<tr>
<td>Low surgical risk</td>
<td>High surgical risk</td>
</tr>
<tr>
<td>Contraindication to fibrinolysis</td>
<td>No contraindication to fibrinolysis</td>
</tr>
<tr>
<td>Recurrent valve thrombosis</td>
<td>First-time episode of valve thrombosis</td>
</tr>
</tbody>
</table>
NYHA class IV | NYHA class I–III
---|---
Large clot (>0.8 cm²) | Small clot (≤0.8 cm²)
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 ≤0.85 cm²/m² 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 cm²/m². 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

<table>
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<tr>
<th>Recommendations for Prosthetic Valve Stenosis</th>
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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 | NEW: Registries and case series have reported on the short-term outcomes and complication rates in patients with bioprosthetic AS |
|        |        | | |
valve-in-valve procedure is reasonable (154,247,248).

who have undergone transcatheter valve-in-valve therapy.

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

<table>
<thead>
<tr>
<th>Recommendations for Prosthetic Valve Regurgitation</th>
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<td><strong>COR</strong></td>
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See Online Data Supplement 23 (Updated From 2014 VHD Guideline)
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.

### Table

| IIa | B-NR | 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). | NEW: 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. |

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

<table>
<thead>
<tr>
<th>Recommendations for IE Intervention</th>
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<td><strong>COR</strong></td>
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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 >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).
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).

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-NR</th>
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<tbody>
<tr>
<td>See Online Data Supplement 24 (Updated From 2014 VHD Guideline)</td>
<td>NEW: 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.</td>
</tr>
</tbody>
</table>

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).

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### Key Words: AHA Scientific Statements
- anticoagulation therapy
- aortic stenosis
- cardiac surgery
- heart valves
- mitral regurgitation
- prosthetic valves
- transcatheter aortic valve replacement
- tricuspid stenosis
- valvular heart disease
## 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)

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<th>Committee Member</th>
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†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)

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*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
References

Nishimura, et al.
2017 AHA/ACC Focused Update on VHD


Nishimura, et al.  
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Circulation, published online March 15, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2017/03/14/CIR.0000000000000503.citation

Data Supplement (unedited) at:
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<thead>
<tr>
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<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
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<tbody>
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<td>• Foundation for Anesthesia Education and Research†</td>
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<tr>
<th>Name</th>
<th>Affiliation</th>
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<th>Thrasos (Steering Committee)*</th>
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<th>Defendant, Myocardial protection, 2014</th>
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AATS indicates American Associate Thoracic Surgery; ACC, American College of Cardiology; AHA, American Heart Association; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; DAPT, dual antiplatelet therapy; DSMB, data safety monitoring board; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health, PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; TRANSLATE-ACS, Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome and VA, Veterans Affairs.
# 2017 AHA/ACC Valvular Heart Disease Focused Update Data Supplement

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## Abbreviation List:

1° indicates primary; 2°, secondary; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AKI, acute kidney injury; AMI, acute myocardial infarction; AP, antibiotic prophylaxis; AS, aortic stenosis; ASA, acetylsalicylic acid; AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; AVR, aortic valve replacement; BHV, bioprosthetic heart valve; BPVT, bioprosthetic valve thrombosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; CTA, computed tomography angiography; CV, cardiovascular; DAPT, dual antplatelet therapy; dx, diagnosis; EF, ejection fraction; ERO, effective regurgitant orifice; heart failure; HR, hazard ratio; HF, FDA, U.S. Food and Drug Administration; HTN, hypertension; Hx, history; IE, infective endocarditis; INR, international normalized ratio; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MAPE, major adverse prosthesis-related events; MCV, Medtronic CoreValve; MDCT, multidetector computed tomography; MHV, mechanical heart valve; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVR, mitral valve repair; N/A, not available; NICE, National Institute for Health and Care Excellence; NVE, native valve endocarditis; NYHA, New York Heart Association; NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; NOAC, novel anticoagulant; OR, odds ratio; ∆P, mean transaortic pressure gradient; PAP, pulmonary artery pressure; pt, patient; PVL, paravalvular leak; PVR, paravalvular regurgitation; PVT, pulmonary valve thrombosis; RCT, randomized controlled trial; RR, relative risk; Rx, prescription; QoL, quality of life; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAF, Stroke Prevention in Atrial Fibrillation; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEE, transthoracic echocardiography; THV, transcatheter heart valve; TIA, transient ischemic attack; TTE, transthoracic echocardiography; VARC, Valvular Academic Research Consortium; VIV: valve-in-valve; VHD, valvular heart disease; VKA, vitamin K antagonist Vmax; and aortic valve maximum velocity.

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### Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of IE (Section 2.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size (N)</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (p values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mackie AS, et al., 2016 (1)</td>
<td>Study type: Retrospective; Size: n=9,431 pts with IE hospitalizations</td>
<td>Inclusion criteria: IE Hospitalizations Exclusion criteria: N/A</td>
<td>1° endpoint: Incidence of IE of hospitalizations per 10 million Results: There was no difference in the rates of hospitalization for IE before and after publication of the revised recommendations</td>
<td>• This retrospective study examined the incidence of IE hospitalizations before and after the 2007 AHA prophylaxis guidelines publication • The rate of IE hospitalizations increased before/after implementation • 2007 AHA recommendations had no impact on incidence rates of hospitalization for IE</td>
</tr>
<tr>
<td>Dayer MJ, et al., 2015 (2)</td>
<td>Study type: Retrospective secular trend study: relationship AP vs. none on IE incidence; Size: Cases reported per 10 million people per mo</td>
<td>Inclusion criteria: Single dose IE prophylaxis all pts w/IE dx Exclusion criteria: N/A</td>
<td>1° endpoint: IE dx at discharge/death and number of Rxs of IE prophylaxis Results: • Decrease IE Prophylaxis; • Increase IE incidence</td>
<td>• AP has fallen and incidence of IE has increased since 2008 NICE guidelines</td>
</tr>
<tr>
<td>Glenny AM, et al., 2013 (3)</td>
<td>Study type: Meta-analysis; Size: Only 1 study met criteria for inclusion</td>
<td>Inclusion criteria: RCT, cohort, case control Exclusion criteria: Guidelines, editorial discussion</td>
<td>1° endpoint: Development of IE, mortality Results: Only 1 study met criteria</td>
<td>• There remains no evidence to determine whether AP is effective or ineffective</td>
</tr>
<tr>
<td>Sherman-Weber S, et al., 2004 (4)</td>
<td>Study type: Retrospective literature review; Size: n=659 pts</td>
<td>Inclusion criteria: Single-center heart transplant hospitalization with IE Exclusion criteria: N/A</td>
<td>1° endpoint: N/A Results: Between 1993-Feb. 2004, 10 pts had endocarditis</td>
<td>• Endocarditis is substantially more common in heart transplant recipients than in general populations. Central venous catheter access and multiple endomyocardial biopsies appear to predispose to infection</td>
</tr>
<tr>
<td>Gillinov AM, et al., 2002 (5)</td>
<td>Study type: Retrospective review; Size: n=22 pts</td>
<td>Inclusion criteria: 22 pts with endocarditis of a previously repaired MV Exclusion criteria: N/A</td>
<td>1° endpoint: N/A Results: 15 had repeat MV operations; 7 were treated with antibiotics</td>
<td>N/A</td>
</tr>
<tr>
<td>Karavas AN, et al., 2002 (6)</td>
<td>Study type: Retrospective review of MV repairs; Size: n=1,275 pts</td>
<td>Inclusion criteria: MV repairs at a single institution Exclusion criteria: N/A</td>
<td>1° endpoint: Endocarditis (non-recurrent) of previously repaired MV Results: 9 of 1,275 pts developed endocarditis after MV repair; all required excision of the annuloplasty ring</td>
<td>N/A</td>
</tr>
<tr>
<td>Duval X, et al.,</td>
<td>Study type: Survey; Size: PtS 25–85 y of age; French</td>
<td>Inclusion criteria:</td>
<td>1° endpoint: N/A Results: A large no. of pts would need prophylaxis to</td>
<td></td>
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<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Aim of Study; Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
<td>Endpoint Results (Absolute Event Rates, p values; OR or RR; &amp; 95% CI)</td>
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<tr>
<td>Mouget FK, et al., 2015; (9) 25758845</td>
<td>Aim: To assess the impact of AP on bacteremia</td>
<td><strong>Inclusion criteria:</strong> 2008 cohort urgent care presentation for tooth extraction.</td>
<td><strong>Intervention:</strong></td>
<td><strong>1° endpoint:</strong> Bacteremia 32% brushing 33% amoxicillin 60% placebo</td>
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<tr>
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<td>Study type: Double-blind, randomized, placebo-controlled</td>
<td><strong>Exclusion criteria:</strong> &lt;10 teeth antibiotic use within 2 wk. Need for AP based on practice guidelines active viral disease, immunocompromised, poorly-controlled systemic disease penicillin allergy, fever, cellulitis, chewing/tooth brushing within 1 h.</td>
<td><strong>Comparator:</strong> Single tooth extraction with placebo</td>
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<td><strong>Size:</strong> n=290 pts</td>
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<tr>
<td>Lockhart PB, et al., 2008; (10) 1851739</td>
<td>Aim: To compare the incidence, duration, type and extent of endocarditis related bacteremia and to determine</td>
<td><strong>Inclusion criteria:</strong> Subjects in need for tooth extraction</td>
<td><strong>Intervention:</strong></td>
<td><strong>1° endpoint:</strong> 32/98 bacterial species identified cause IE. Cumulative incidence from 6 blood draws</td>
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<tr>
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<td><strong>Study type:</strong> Observational case control</td>
<td><strong>Exclusion criteria:</strong></td>
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<tr>
<td></td>
<td><strong>Size:</strong> n=273 cases (238 native valve infections, 35 prosthetic valve infections)</td>
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</table>

Strom BL, et al., 1998; (8) 9841581

**Study type:** Observational case control

**Size:** n=273 cases (238 native valve infections, 35 prosthetic valve infections)

**Inclusion criteria:** Subjects with community acquired IE discharged within 3 mo and matched community residents

**Exclusion criteria:** IE due to IV drug abuse, <18 y of age, hospital acquired IE

**1° endpoint:** N/A

**Results:**
- Dental treatment not more common in cases compared to controls (adjusted OR: 0.8, 95% CI: 0.4–1.5)
- Cases with Hx of MV prolapse OR: 19.4; congenital heart disease OR: 6.7, valvular surgery OR: 74.6, rheumatic fever OR: 13.4; heart murmur OR: 4.2
- Prophylaxis dental therapy was significantly low (p=0.03) in cases with cardiac lesions as compared to controls.

**2° endpoint:** N/A

**Results:**
- Avoid 1 case of IE
- The results cannot be generalized to general population

**Study Acronym:** RCTs for IE (Section 2.4)
the impact of AP on single tooth extraction.

**Study type:** RCT

**Size:** n=290 pts

Use of systematic antibiotics within previous 2 wk; on AP; active viral disease; immunocompromised; systemic disease with bad prognosis; Hx of penicillin allergy; 100.5°F temp; facial cellulitis; and handling of the gingival tissues within 1 h before the study.

- Extraction with Placebo group (96)

• Tooth brushing: 23%, extraction-amoxicillin: 33% and extraction-placebo: 60%; p<0.0001
• Amoxicillin resulted in decrease of positive cultures (p=0.05)

1° Safety endpoint (if relevant): N/A

at risk individuals for IE

## Data Supplement 3. RCTs Comparing Anticoagulation for AF in Patients With VHD (Section 2.4.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, p values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARISTOTLE</strong> Avezum A, et al., 2015 (11) 26106009</td>
<td><strong>Aims:</strong> Apixaban vs. warfarin in pts with VHD  <strong>Study type:</strong> Sub-analysis of prospective, multicenter, randomized  <strong>Size:</strong> n=4,808 pts (26.4%) had a Hx of VHD (all types of VHD, except severe MS)</td>
<td><strong>Inclusion criteria:</strong>  ● Pts with VHD, including AS, AR, mild MS, MR, tricuspid stenosis, tricuspid regurgitation, valve repair, or bioprosthetic valve replacement  <strong>Exclusion criteria:</strong>  ● Clinically significant MS  ● Indications for oral anticoagulation other than AF  ● Planned use of concomitant high-dose ASA (&gt;165 mg/d) or DAPT</td>
<td><strong>Intervention:</strong> Apixaban  <strong>Comparator:</strong> Warfarin</td>
<td><strong>1° endpoint:</strong> Stroke or systemic embolism  <strong>Safety endpoint:</strong> Major bleeding as defined by the International Society on Thrombosis and Haemostasis</td>
<td>• VHD pts in this subgroup of Aristotle (n=4,808) were older, more prior MI and bleeding; and higher CHADS2 scores  • Pts with VHD experienced similar benefit with anticoagulation  • Apixaban was associated with less bleeding</td>
</tr>
<tr>
<td><strong>ROCKET AF</strong> Breithardt G, et al., 2014 (12) 25148838</td>
<td><strong>Aims:</strong> Assess outcomes of pts with VHD in ROCKET-AF Rivaroxaban vs. Warfarin  <strong>Study type:</strong> Sub-analysis of prospective, multicenter, randomized  <strong>Size:</strong> n=2,003 pts (14.1%) had VHD</td>
<td><strong>Inclusion criteria:</strong> Nonvalvular AF (with no MS, no heart valve prosthesis, and no valvular disease requiring surgery)  <strong>Exclusion criteria:</strong>  ● Hemodynamically significant mitral valve stenosis.  ● Prosthetic heart valve  ● Annuloplasty with or without prosthetic ring  ● Planned invasive procedure with potential for uncontrolled bleeding</td>
<td><strong>Intervention:</strong> Rivaroxaban  <strong>Comparator:</strong> Warfarin</td>
<td><strong>1° endpoint:</strong> Composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism  <strong>Safety endpoint:</strong> Major or non-major bleeding or intracranial hemorrhage</td>
<td>• Risk of stroke is similar to pts without VHD  • Efficacy of rivaroxaban vs. warfarin was similar in pts with and without significant valvular disease</td>
</tr>
</tbody>
</table>
### NASPEAF

**Perez-Gomez F, et al., 2004 (13) 15489085**

| **Aim:** To evaluate the safety and efficacy of combining antiplatelet and moderate intensity anticoagulation therapy in pts with AF |
| **Study type:** Multicenter RCT |
| **Size:** n=1,209 pts, 13 hospitals |
| **Inclusion criteria:** Pts with chronic or documented paroxysmal AF |
| **Exclusion criteria:**  |
| - Low-risk pts according to SPAF III stratification |
| - Pts <60 y of age |
| - Mechanical valve prosthesis, |
| - Stroke in the previous 6 mo |
| - Serum creatinine over 3 mg/dl, |
| - Alcoholism or drug addiction, |
| - Severe uncontrolled HTN |
| - Diffuse arteriosclerosis, |
| - Indication for NSAIDs or indication/contraindication for antiplatelet or anticoagulant therapy |
| **Intervention:** The high-risk group pts either had anticoagulation (acenocoumarol) with a target INR of 2–3 or the combination therapy with a target INR of 1.4–2.4. |
| **Comparator:** The intermediate-risk group had 3 arms; oral anticoagulation (acenocoumarol) to a target INR of 2–3, triflusal 600 mg daily, or a combination of both with a target INR of 1.25–2. |
| **1° endpoint:** The presence of vascular death, TIA, and nonfatal stroke or systemic embolism, (whichever event came first) |
| - 1° outcome was lower in the combined therapy than in the anticoagulant arm in both the intermediate (HR: 0.33; 95% CI: 0.12–0.91; p=0.02) and the high-risk group (HR: 0.51; 95% CI: 0.27–0.96; p=0.03). |
| **Safety endpoint:** N/A |

### RE-LY Sub-analysis

**Ezekowitz, et al. 2016 (14) 27496855**

| **Aim:** Compare pts with and without any valve disease and to compare warfarin or dabigatran |
| **Study type:** Post hoc analysis |
| **Size:** n=3,950 pts with any VHD |
| **Inclusion criteria:** VHD and AF |
| **Exclusion criteria:** Prosthetic heart valves, significant MS, and VHD requiring intervention |
| **Intervention:** Warfarin |
| **Comparator:** Dabigatran |
| **1° endpoint:** The presence of VHD did not influence comparison of dabigatran at either dose with warfarin in terms of stroke or systemic embolism, major bleed, death, or intracranial hemorrhage. |
| **Safety endpoint:** N/A |

- The combination of antiplatelet and anticoagulation therapy significantly decreased vascular events compared to anticoagulation only and was safe in AF pts.
## Data Supplement 4.  Nonrandomized Trials, Observational Studies, and/or Registries of Anticoagulation for AF in Patients With VHD (Section 2.4.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (p values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noseworthy PA, et al., 2016 (15)</td>
<td>Study type: Retrospective analysis of administrative claims data to compare effectiveness and safety of NOACs with warfarin in pts with AF and VHD</td>
<td>Inclusion criteria: Pts with VHD and AF</td>
<td>1° endpoint: N/A</td>
<td>Combining rheumatic and nonrheumatic MS, NOACs trended toward lower risk of stroke (HR: 0.52 95% CI: 0.15–1.81, p=0.31) and major bleeding (HR: 0.77 95% CI: 0.41–1.43, p=0.40). Pts with AS or AR or MR both stroke or systemic embolism and major bleeding were significantly lower in NOACs compared to warfarin</td>
</tr>
<tr>
<td></td>
<td>Size: n=20,158 NOAC-treated pts with VHD</td>
<td>Exclusion criteria: /A</td>
<td>Results: N/A</td>
<td></td>
</tr>
<tr>
<td>Olesen, et al., 2011 (16) 21282258</td>
<td>Study type: Nationwide cohort study</td>
<td>Inclusion criteria: Nonvalvular AF</td>
<td>1° endpoint: To evaluate the individual risk factors composing the CHADS2 score and the CHA2DS2-VASc score and to calculate the capability of the schemes to predict thromboembolism.</td>
<td>CHA2DS2-VASc performed better than CHADS2 in predicting pts at high risk and low risk</td>
</tr>
<tr>
<td></td>
<td>Size: n=121,280 pts; 73,538 included in analysis</td>
<td>Exclusion criteria: No previous diagnoses of MV or AV disease, and no MV or AV surgery</td>
<td>Results: • In pts at low risk, 1.67 per 100 person y (95% CI:1.47–1.89) • In pts at intermediate risk, 4.75 per 100 person y (95% CI:4.45–5.07)</td>
<td></td>
</tr>
<tr>
<td>Petty, et al., 2000 (17) 11062286</td>
<td>Study type: Cohort/epidemiological</td>
<td>Inclusion criteria: Echocardiographic dx of MS (n=19), MR (n=528), AS (n=140), and AR (n=106) between 1985 and 1992</td>
<td>1° endpoint: Rates and determinants of cerebrovascular events in pts with VHD pts.</td>
<td>Independent predictors of CVA were age, AF, and severe AS. AS was associated with rates of CVA similar to those for MS and was an independent determinant of CVA events after adjustment for age and AF (RR:3.5)</td>
</tr>
<tr>
<td></td>
<td>Size: n=729 pts</td>
<td>Exclusion criteria: N/A</td>
<td>Results: Risk of CVA and death among pts with valve disease was significantly higher than significantly higher than the corresponding age- and sex-adjusted rates for the community</td>
<td></td>
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<tr>
<td>Study</td>
<td>Aim of Study</td>
<td>Study Type</td>
<td>Study Groups (N)</td>
<td>Patient Population</td>
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<tr>
<td>PARTNER COHORT A (high-surgical risk)</td>
<td>To show that TAVR is not inferior to SAVR</td>
<td>RCT</td>
<td>TAVR 348 vs. SAVR 351</td>
<td>Severe symptomatic calcific AS defined as AVA &lt;0.8 cm² plus a ΔP&gt;40 mm Hg or Vmax ≥4.0 m/s with NYHA class II-IV symptoms.</td>
</tr>
<tr>
<td>Smith et al 2011 21638911 (18)</td>
<td></td>
<td></td>
<td>TAVR was transfemoral in 244 and transapical in 104</td>
<td>High surgical risk defined as ≥15% risk of death by 30 d after the procedure. An STS score ≥10% was used for guidance with an actual mean STS score of 11.8±3.3%.</td>
</tr>
<tr>
<td>Kodali, et al. 2012 22443479 (19)</td>
<td></td>
<td></td>
<td></td>
<td>Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF&lt;20%, aortic annulus &lt;18 or &gt;25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency</td>
</tr>
<tr>
<td>Mack, et al. 2015 25788234 (20)</td>
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<tr>
<td>PARTNER COHORT B (inoperable)</td>
<td>Compare TAVR to medical Rx in inoperable pts with severe symptomatic AS</td>
<td>RCT</td>
<td>TAVR in 179 vs. standard medical therapy in 179 (including BAV in 150 (84%))</td>
<td>Severe symptomatic calcific AS defined as AVA &lt;0.8 cm² plus a ΔP&gt;40 mm Hg or Vmax ≥4.0 m/s with NYHA class II-IV symptoms.</td>
</tr>
<tr>
<td>Kapadia, et al 2015 25788231 (21)</td>
<td></td>
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<td>Inoperable due to coexisting conditions with predicted ≥50% risk of death within 30 d of intervention or a serious irreversible condition.</td>
</tr>
<tr>
<td>Leon, et al 2010 40961243 (22)</td>
<td></td>
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<td>Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF&lt;20%, aortic annulus &lt;18 or &gt;25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency</td>
</tr>
<tr>
<td>Makkar, et al 2012 22443478 (23)</td>
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<tr>
<td><strong>Core Valve</strong> (high surgical risk)</td>
<td>Compare TAVR and SAVR in pts at high surgical risk</td>
<td>RCT</td>
<td>TAVR with self-expanding Core Valve prosthesis in 390 vs. SAVR in 357. Mean age 83.2 y. Men 52.7% Mean STS-PROM score 7.4%</td>
<td>Severe symptomatic calcific AS defined as AVA ≤0.8 cm², or indexed AVA ≤0.5 cm²/m² and either a ∆P &gt;40 mm Hg or Vmax &gt;4.0 m/s with NYHA class II-IV symptoms. High surgical risk defined as ≥15% risk of death by 30 d after the procedure and a risk or death or irreversible complications &lt;50% within 30 d of procedure</td>
</tr>
</tbody>
</table>

| **PARTNER 2 COHORT A** | To compare surgical AVR and TAVR in an intermediate risk cohort | RCT | TAVR 1011 pts vs. SAVR 1021 pts TAVR was transfemoral in 76.3% and transapical in 23.7% | Severe symptomatic calcific AS defined as AVA <0.8 cm² plus a ∆P>40 mm Hg or Vmax ≥4.0 m/s with NYHA class II-IV symptoms. Intermediate surgical risk defined as ≥24% risk of death by 30 d after the procedure. An STS score ≥8% was the upper limit of enrolled pts. Pts with an STS score <4% were enrolled if other conditions indicating increased risk. Mean STS score was 5.8%. Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency | 1° endpoint cause death or disabling stroke at 2 y: HR: 0.89 (95% CI: 0.73–1.09; p=0.25). All-cause death at 2 y: TAVR 16.7% vs. SAVR 18.0% Disabling Stroke TAVR 6.2% vs. SAVR 6.4% Transfemoral TAVR vs SAVR: HR: 0.79; 95% CI: 0.62–1.00; p=0.05 Transthoracic TAVR vs SAVR: HR: 1.21; 95% CI: 0.84–1.74; p=0.31 | • Life-threatening bleeding: TAVR 10.4% vs. SAVR 43.4%, p<0.001 | • Acute kidney injury: TAVR 1.3% vs. SAVR 3.1%, p=0.006 | • New-onset AF: TAVR 9.1% vs. SAVR 26.4%, p<0.001 | • Repeat Hospitalization: TAVR 19.6% vs. SAVR 17.3%; p=0.22 | • Permanent Pacer within 30 d: TAVR 8.5% vs SAVR 6.9%; p=0.17 |
| Leon, et al. 2016 | 27040324 | (26) | | | |

| **NOTION** (severe symptomatic AS with low-surgical risk) | Compare outcomes with TAVR and SAVR in pts at low surgical risk | RCT | TAVR with self-expanding Core Valve prosthesis in 145 vs. SAVR in 135 Mean age: 79.12 y. Men: 53.2% STS-PROM score <4 in 81.8% | Severe symptomatic calcific AS in pts over age 70 y with no significant coronary disease. Severe AS defined as AVA <1.0 cm² or indexed AVA ≤0.6 cm²/m² plus a ∆P >40 mm Hg or Vmax >4.0 m/s with NYHA class II-IV symptoms. Also include asymptomatic severe AS (n=10) if severe LV hypertrophy, decreasing LVEF or new onset AF present. Exclusions were expected survival <1 y, other severe valve disease, significant coronary disease, previous cardiac surgery, MI or stroke within 30 d, severe renal or pulmonary disease. | Composite endpoint: Death from any cause, stroke, or MI at 1 y. TAVR 13.1% vs. SAVR 16.3% ( -3.2% absolute difference, p=0.43 for superiority). | Major vascular complications at 30 ds: TAVR 5.6% vs. SAVR 1.5% (p=0.10) | Major bleeding at 30 ds: TAVR 29.5% vs. SAVR 36.7% (p=0.03) | AKI: TAVR 0.7% vs. SAVR 6.7% (p=0.01) | Permanent pacer implantation at 30 d: TAVR 34.13% vs. SAVR 1.6% (p<0.001) | New-onset or worsening AF at 30 d: TAVR 16.9% vs. SAVR 57.8% (p<0.001) |
| Thyregod HG, et al. 27005980 | (27) | | | | |
Horstkotte, et al  1988  3042404 (28)  

Compare outcomes with symptomatic vs. asymptomatic severe AS  Retrospective  n=35 pts  Severe symptomatic AS refused AVR. AVA 0.4–0.8 cm²  Mean interval from symptom onset to death: 4.5 y for angina (n=18), 2.6 y for syncope (n=13), <1 y for HF (n=20)  Mortality reached 100% at: 10 y for angina, 5 y for syncope, 2.4 y for HF  There were 3 sudden deaths before symptom onset

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of TAVR (Section 3.2.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
<th>Comment(s)</th>
</tr>
</thead>
</table>
| Popma, et al. 2014 (29) 24657695 | Study type: Prospective, multicenter  
Size: n=506 pts recruited; n=489 pts who underwent attempted treatment with CoreValve THV  
Inclusion criteria: Pts with symptomatic severe AS with prohibitive risk for surgery  
Exclusion criteria: N/A | 1° endpoint: All-cause mortality or major stroke at 12 mo, compared to a pre-specified objective performance goal  
Results: All-cause mortality or stroke was 26.0% vs. 43.0% objective performance goal (p<0.0001) | • TVR with self-expanding bio prosthesis was found to be safe for pts with symptomatic severe AS with prohibitive risk for surgery |
| Thourani, et al. 2016 (30) 27053442 | Study type: Observational  
Size: n=1,077 pts at 51 sites  
Inclusion criteria: Pts receiving TAVR with the SAPIEN 3 valve compared to intermediate risk pts treated with surgical valve replacement in the PARTNER 2A trial.  
Exclusion criteria: N/A | 1° endpoint: All-cause mortality, stroke, reintervention, and aortic valve regurgitation 1 y following plantation.  
Results: TAVR was noninferior (9.2%; 90% CI: -12.4–6; p<0.0001) and superior (-9.2%, 95% CI: -13.0 – -5.4; p<0.0001) to surgical valve replacement. | • TAVR with SAPIEN 3 was associated with lower all-cause mortality, strokes, and aortic valve regurgitation at 1 y compared with surgical valve replacement of the PARTNER 2A trial. |

Data Supplement 17. (Updated From 2014 Guideline) Primary MR—Evidence for Intervention (Section 7.3.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Tribouilloy, et al. 1999 (31) 9918527 | Assess impact of symptom status on outcome  
Retrospective  
n=478 pts | Mitral surgery | NYHA class I,II, III, IV | Advanced preoperative symptoms increased operative mortality by 10-fold. Long-term survival also reduced. |
| Gillinov, et al. 2010 (32) 20667334 | Assess impact of symptoms on outcomes  
Retrospective propensity-matched  
n=4,253 pts | MVR | NYHA all class | Even NYHA class II preoperative symptoms impaired late survival. |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Title</th>
<th>Study Design</th>
<th>Study Group</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenhek et al. 2006 (33) 16651470</td>
<td>Assess outcome with watchful waiting</td>
<td>Prospective</td>
<td>n=132 pts</td>
<td>Watchful waiting for severe MR</td>
</tr>
<tr>
<td>Kang et al. 2009 (34) 19918506</td>
<td>Assess outcome with watchful waiting</td>
<td>Prospective</td>
<td>n=447 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>Enriquez-Sarano et al. 1994 (35) 8044955</td>
<td>Assess predictors of outcome</td>
<td>Retrospective</td>
<td>n=409 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>Tribouilloy et al. 2009 (36) 19909877</td>
<td>Assess impact of LVESD on outcome</td>
<td>Retrospective</td>
<td>n=739 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>Enriquez-Sarano et al. 2005 (37) 15745978</td>
<td>Assess impact of MR severity</td>
<td>Prospective</td>
<td>n=450 pts</td>
<td>N/A</td>
</tr>
<tr>
<td>Ghoreishi 2011 (38) 21962906</td>
<td>Assess impact of pulmonary HTN on outcome</td>
<td>Retrospective</td>
<td>n=873 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>Goldman et al. 1987 (39) 3624663</td>
<td>Compare LV function after replace vs. repair</td>
<td>Prospective</td>
<td>n=18 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>David et al. 1984 (40) 6492840</td>
<td>Compare outcome with and without chordal presentation</td>
<td>Prospective</td>
<td>n=27 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>Rozich et al. 1992 (41) 1451243</td>
<td>Examined LVEF</td>
<td>Retrospective</td>
<td>n=15 pts</td>
<td>Mitral surgery</td>
</tr>
<tr>
<td>David et al. 2013 (42) 23459614</td>
<td>Assess long-term Outcome of MV repair</td>
<td>Retrospective</td>
<td>n=804 pts</td>
<td>Mitral repair</td>
</tr>
<tr>
<td>Tribouilloy et al. 2011 (43) 21821606</td>
<td>Assess predictors of post op LV function</td>
<td>Retrospective</td>
<td>n=355 pts</td>
<td>Mitral surgery</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>n</th>
<th>Procedure</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suri, et al. 2016 (44)</td>
<td>Retrospective</td>
<td>n=1,218 pts</td>
<td>Mitral repair</td>
<td>Repair Durability: 83% freedom of moderate MR at 10 y; 96% for posterior leaflet disease; 2% need for re-op after 1996</td>
</tr>
<tr>
<td>Vassileva, et al. 2013 (45)</td>
<td>Retrospective</td>
<td>n=47,279 pts</td>
<td>Mitral repair</td>
<td>Repair vs. replacement: Survival following repair superior to Replacement and not different from a normal population</td>
</tr>
<tr>
<td>Suri, et al. 2013 (46)</td>
<td>Retrospective</td>
<td>n=2,097 pts</td>
<td>Mitral repair</td>
<td>Early vs. Triggered MV Surgery: Survival in Propensity Matched Pts was superior in those operated before classic Triggers</td>
</tr>
<tr>
<td>Dillon, et al. 2015 (47)</td>
<td>Retrospective</td>
<td>n=366 pts</td>
<td>Mitral repair</td>
<td>Repair vs. Nonrheumatic MR: In the 41% of rheumatic MR pts where repair was attempted, results were similar to nonrheumatic pts with an 81% freedom of failure at 10 y</td>
</tr>
<tr>
<td>Feldman, et al 2015 (48)</td>
<td>Prospective RCT</td>
<td>n=279 pts</td>
<td>Mitral repair</td>
<td>Percutaneous vs Surgical Repair: Initial failure greater in the percutaneous group but failure after 6 mo was identical for percutaneous vs. surgical repair</td>
</tr>
<tr>
<td>Grigioni, et al. 2008 (49)</td>
<td>Prospective</td>
<td>n=394 pts</td>
<td>Mitral surgery</td>
<td>Repair vs. replacement vs. nonsurgery: 92% 54-y survival for repair; 80% for replacement.</td>
</tr>
<tr>
<td>Gillinov, et al. 2008 (50)</td>
<td>Prospective</td>
<td>n=328 pts</td>
<td>N/A</td>
<td>Repair vs. replacement propensity: 5, 10, 15 y survival 95, 87, 68 repair vs. -80, 60, 44 replacement.</td>
</tr>
<tr>
<td>Weiner, et al. 2014 (51)</td>
<td>Retrospective</td>
<td>n=1,054 pts</td>
<td>Mitral repair</td>
<td>Early experience vs late: As experience improved over time, morbidity and LOS decreased</td>
</tr>
<tr>
<td>Enrique Serano, et al. 2015 (52)</td>
<td>Retrospective stratification</td>
<td>n=1,512 pts</td>
<td>Mitral surgery correction</td>
<td>Surgical indication class I triggers (HF symptoms, EF &lt;60%, end-systolic diameter &gt;40 mm vs. class II (AF or pulmonary HTN) vs. early class III (combination of severe MR and high probability of valve repair). Operative mortality highest with Class I (1.1% vs. 0% and 0%, p=0.016). Long-term survival was lower with Class I (15-y 42% ± 2%; adjusted HR: 1.89 (95% CI: 1.53, 2.34), p&lt;.0001) and ClassII-CompT (15-y 53% ± 4%, adjusted HR: 1.39 (95% CI: 1.04, 1.84), p=0.027) vs. Class II-EarlyT (15-y 70% ± 9%, p&lt;0.0001).</td>
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</table>
Suri, et al. 2008 (53)  
**Examine early changes in LV size and function after MV repair or replacement**  
Retrospective  
n=861 pts  
Mitr al repair/replacement  
N/A  
Rate of valve repair increased from 78% to 92%. At early echocardiography (mean, 5 d postop), significant decreases in LVEF (mean: 28.8) and LVESD (mean, 27.5). Magnitude of early decline in EF was similar in pts who had MVR and MV replacement.

Quintana, et al. 2014 (54)  
**Assess predictors and long-term survival of latent LV dysfunction**  
Retrospective  
n=1,705 pts  
Mitr al repair  
Presence vs. absence of early postop LV dysfunction (LVEF <50%)  
Pts with absence of LV dysfunction had significant and immediate greater enlargement in systolic dimension and decrease in right ventricular systolic pressure. EF recovered to preop levels (>60%) in only one third of pts with postrepair EF<50% vs. two thirds of those with an EF of ≥50% (p<001). The overall survival at 5, 10, and 15 y of follow-up was 95%, 85%, and 70.8%, respectively. Postop EF <40% conferred a 70% increase in the hazard of late death: adjusted HR: 1.74 (95% CI: 1.03, 2.92), p=0.037

Suri, et al. 2011 (55)  
**To assess the tempo of MR progression, predictors of MR progression, incidence of de novo LV dysfunction, and predictors of LV dysfunction**  
Retrospective observational study  
n=142 pts  
N/A  
- The likelihood of MR progression was higher in those with greater baseline MR grade (mild/mild-moderate 44/124 (31%) vs. moderate/moderate-severe 35/60 (58%) p=0.0008).
- LV deterioration occurred even in the absence of MR progression
- Multivariable modeling revealed that LVEDD was the only independent predictor OR: 1.15; 95% CI: 1.08, 1.23; p=0.0001 of greater MR progression with time.

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**Data Supplement 18. (Updated From 2014 Guideline) Secondary MR—Evidence for Intervention (7.4.3)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, et al 2006 (56) 16820626</td>
<td>Outcome surgery in moderate-to-severe ischemic MR</td>
<td>Retrospective</td>
<td>n=107 pts</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>Higher operative mortality with CABG and MV repair vs CABG alone (12% vs. 2%) but similar 5 y survival (88% vs87%)</td>
</tr>
<tr>
<td>Rossi, et al 2011 (57) 21907656</td>
<td>Impact of on outcome</td>
<td>Retrospective</td>
<td>n=1,256 pts</td>
<td>None</td>
<td>Impact of SMR on HF</td>
<td>After adjusting for LVEF and other factors-SMR increased mortality by 2-fold</td>
</tr>
<tr>
<td>Wu, et al 2005 (58) 15680716</td>
<td>Impact of surgery on moderate-severe MR</td>
<td>Retrospective</td>
<td>n=126 pts</td>
<td>Surgery with mitral annuloplasty</td>
<td>Med Rx</td>
<td>No survival advantage to MV annuloplasty</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Title</th>
<th>Study Design</th>
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<th>Procedure</th>
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<th>Key Findings</th>
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<tr>
<td>Mihaljevic, et al 2007 (59) 17543639</td>
<td>Impact of mitral surgery moderate- severe on SMR</td>
<td>Retrospective</td>
<td>n=290 pts</td>
<td>CABG+ MV surgery</td>
<td>CABG</td>
<td>1-, 5-, 10-y survival -88, 75, 47 CABG vs. 92, 74, 39 CABG + MV symptoms; (p=NS) functional class improved equally in both groups</td>
</tr>
<tr>
<td>Benedetto, et al 2009 (60) 19377377</td>
<td>Impact of MV surgery on SMR</td>
<td>Meta-analysis</td>
<td>n=2,479 pts</td>
<td>CAGB+MV surgery</td>
<td>CABG</td>
<td>No difference in survival or symptomatic status</td>
</tr>
<tr>
<td>Fattouch, et al 2009 (61) 19619766</td>
<td>Impact of MV surgery in ischemic MR</td>
<td>Randomized prospective</td>
<td>n=102 pts</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>No difference in mortality. Repair group had reduced cardiac dimensions and symptoms vs. CABG alone</td>
</tr>
<tr>
<td>Deja, et al 2012 (62)</td>
<td>Impact of repair in ischemic MR</td>
<td>Randomized prospective</td>
<td>n=104 pts</td>
<td>CABG + repair</td>
<td>CABG</td>
<td>53% mortality CABG, vs. 43% mortality CABG + MVR (p=NS); after adjustment CABG + MVR had better survival</td>
</tr>
<tr>
<td>Nombela-Franco, et al. 2014 (63)</td>
<td>Summarize the effect of TAVR on MR</td>
<td>Retrospective &gt;1,000</td>
<td>TAVR</td>
<td>MR before and after TAVR</td>
<td>Change in MR quite variable</td>
<td></td>
</tr>
<tr>
<td>Smith PK, et al. 2014 (64) 25405390</td>
<td>Compare CABG to CABG +</td>
<td>Randomized prospective</td>
<td>n=301 pts</td>
<td>CABG</td>
<td>CABG + Repair</td>
<td>Adding repair increased morbidity but did not improve LV geometry</td>
</tr>
<tr>
<td>Michler, et al. 2016 (65) 27040451</td>
<td>Compare CABG to CABG + MV repair in pts with moderated ischemic MR</td>
<td>Randomized prospective</td>
<td>n=301 pts</td>
<td>CABG</td>
<td>CABG + Repair</td>
<td>2-y follow up: In pts with moderate ischemic MR undergoing CABG, the addition of MVR did not lead to significant differences in LV reverse remodeling at 2 y. MVR provided a more durable correction of MR but did not significantly improve survival or reduce overall adverse events or readmissions and was associated with an early hazard of increased neurologic events and supraventricular arrhythmias.</td>
</tr>
<tr>
<td>Acker, et al 2014 (66)</td>
<td>Compare repair to replacement in severe 2° MR</td>
<td>Randomized prospective</td>
<td>n=251 pts</td>
<td>repair</td>
<td>Replacement</td>
<td>There was no significant difference in LV reverse remodeling or survival at 12 mo between pts who underwent MVR and those who underwent MV replacement. Replacement provided a more durable correction of MR, but there was no significant between-group difference in clinical outcomes.</td>
</tr>
<tr>
<td>Goldstein, et al 2016 (67) 26550689</td>
<td>Compare repair to replacement in 2° MR</td>
<td>Randomized prospective</td>
<td>n=251 pts</td>
<td>repair</td>
<td>Replacement</td>
<td>High and equal mortality in both groups with greater recurrent in with repair</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Size</td>
<td>Methods</td>
<td>Patient Population</td>
<td>Follow-Up</td>
<td>Outcomes</td>
<td>Study Limitations</td>
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<tr>
<td>Hammermeister, et al 2000 (68) 11028464</td>
<td>575 pts undergoing isolated AVR (394) or MVR (181) at 13 VA medical centers (1977–1982)</td>
<td>RCT</td>
<td>Isolated AVR or MVR. Concurrent CABG performed in 39% of AVR and 36% of MVR pts. Women, contraindications to VKA anticoagulation, requirement for antiplatelet therapy, valve size AVR or endocarditis.</td>
<td>15 y</td>
<td>• AVR, all-cause mortality at 15 y was lower for MHV vs. BHV: (66±3% [mean±SE] vs. 79±3%; p=0.02) No difference for MVR. • 1° valve failure was significantly greater with a BHV vs. MHV valve, both for AVR (23±5% vs. 0±0%; p=0.0001) and MVR (44±8% vs. 5±4%; p=0.0002). 1° valve failure nearly always (93%) occurred in pts &lt;65 y. • AVR reoperation was higher after BHV vs. MHV (29±5% vs. 10±3%; p=0.004). No statistically significant difference for MVR.</td>
<td>Pts receiving mechanical MVR were older and had more HTN than those with a bioprosthetic MVR.</td>
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<tr>
<td>Oxenham, et al. 2003 (69) 12807838</td>
<td>541 pts undergoing MVR (261), AVR (211), or both (61) 1975–1979</td>
<td>RCT</td>
<td>Mean age 53.9 (10.6) y. 56% female. Additional valve procedures or not eligible for VKA anticoagulation.</td>
<td>20 y</td>
<td>• No difference in overall survival (Bjork-Shiley vs. porcine prosthesis [mean (SEM)]; 25.0 (2.7)% vs. 22.6 (2.7)%, log rank test p=0.39. • Combined endpoint of death and reoperation occurred in 23.5 (2.6)% with BHV vs. 6.7 (1.6)% with MHV (log rank test p&lt;0.0001). • Major bleeding was more common in pts with MHV (40.7 [5.4]% vs. 27.9 [8.4]% after 20 y; p=0.008), with NS difference in major embolism or endocarditis.</td>
<td>Older generation valve types.</td>
</tr>
<tr>
<td>Stassano, et al. 2009 (70) 19892237</td>
<td>310 pts undergoing AVR 1995–2003</td>
<td>RCT</td>
<td>Age 55–70 y Other valve surgery. Contraindication to VKA anticoagulation</td>
<td>Mean 106±28 mo</td>
<td>• No survival difference at 13 y between BHV and MHV groups. • Valve failures and reoperations were more frequent in the BHV group compared with the MHV group (p=0.0001 and p=0.0003, respectively). • No differences in the linearized rate of thromboembolism, bleeding, endocarditis, and MAPE between the MHV and BHV valve groups.</td>
<td>Power may not be adequate to detect a clinically-meaningful difference at longer follow-up.</td>
</tr>
<tr>
<td>Khan, et al 2001 (71) 11479498</td>
<td>Initial AVR in 1389 pts, MVR in 915 pts, 1976–2001 at a single medical center.</td>
<td>Retrospective, observational</td>
<td>Age 64.5±12.9 y for MHV Age 72.0±12.6 y for BHV Homografts, combined MHV and BHV procedure, any previous valve surgery</td>
<td>20 y</td>
<td>• Freedom from reoperation at 15 y for AVR was 67±4.8% for BHV and 99±0.5% for MHV. For MVR, freedom from reoperation was 52±5.7% for BHV and 93±3.2% for MHV. • Survival at 15 y (BHV vs. MHV, p=NS for all): • AVR in pts &lt;65 y (56±5.9 vs. 61±5.3%), AVR in pts &gt;65 y (17±3.4 vs. 17±3.9%). • MVR in pts &lt;65 y (32±5.5 vs. 51±5.4%), MVR in pts &gt;65 y (12±3.5 vs. 18±3.8%)</td>
<td>Not prospective, not randomized. Concurrent CABG in 50%.</td>
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<tr>
<td>Study Reference</td>
<td>Study Details</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Follow-up</td>
<td>Results</td>
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<tr>
<td>Chan, et al. 2006</td>
<td>3,063 pts undergoing AVR 1982–1998</td>
<td>Retrospective observational</td>
<td>2,195 BHV and 980 MHV.</td>
<td>Previous cardiac surgery</td>
<td>Average follow-ups in y for the BHV and MHV groups were 7.5±4.7% and 5.0±3.3% (p&lt;0.001), respectively.</td>
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<td>• Valve-related mortality (per pt-y): BHV 1.0% vs. MHV 0.7%</td>
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<td>• Valve-related reoperation (per pt-y): BHV 1.3% vs. MHV 0.3% (p&lt;0.001)</td>
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<td>• Valve-related morbidity: BHV 0.4% vs. MHV 2.1% (p&lt;0.001)</td>
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<td>• Actual freedom from valve-related reoperation favored MHV for pts &lt;60 y. Actual freedom from valve-related morbidity favored BHV for pts &gt;40 y. Actual freedom from valve-related mortality was similar for BHV vs. MHV &gt;50 y.</td>
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<tr>
<td>Kulik, et al. 2006</td>
<td>659 pts age 50–65 y with initial AVR or MVR</td>
<td>Prospective, observational</td>
<td>AVR in 388 (MHV 306, BHV 48). MVR in 236 (MHV 188, BHV 48).</td>
<td>Enrolled only if survived perioperative period. Valve repair excluded.</td>
<td>Mean 5.1±4.1 y; maximum 18.3 y</td>
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<td>• Freedom from 1° endpoint MAPE at 10 y (reoperation, endocarditis, major bleeding, or thromboembolism):</td>
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<td>• AVR MHV 70±4.1% vs. BHV 41.0±30.3% (p=0.55) MVR MHV 53.2±8.6% vs. BHV 61.2±9.2% (p=0.34)</td>
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<tr>
<td>Ruel, et al., 2007</td>
<td>567 pts undergoing AVR or MVR</td>
<td>Retrospective observational</td>
<td>Age &lt;60 y. First heart valve operation.</td>
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<td>Mean survivor follow-up, 24.0±3.1 y</td>
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<td>• Survival in AVR: no difference between BHV vs. MHV (HR:0.95, 95% CI: 0.7–1.3);</td>
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<td>• Survival in MVR: no difference between BHV or MHV (HR: 0.9, 95% CI: 0.5–1.4);</td>
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<td>• Long-term survival worse in MVR than AVR (HR: 1.4, 95% CI: 1.1–1.8);</td>
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<td>• Reoperation in 89% of BHV AVR and 84% of BHV MVR (older generation devices) with reoperative mortality 4.3%.</td>
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<td>• Simulated events for a 60-y man undergoing AVR, favors a BP vs. MP:</td>
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<td>• life-expectancy: 11.9 vs. 12.2 y,</td>
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<td>• event-free survival: 9.8 vs. 9.3 y,</td>
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<td>• reoperation-free: 10.5 vs. 11.9 y,</td>
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<td>• reoperation risk: 25% vs. 3%,</td>
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<td>• risk of bleeding: 12% vs. 41%</td>
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<td>• At a median 4-y follow-up, thromboembolism was 0.77% for MP and 0.78% for BP (p=NS)</td>
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<td>• There was a survival benefit of mechanical prostheses at 7.5 y</td>
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<td>• Noninferiority to bioprosthetic AVR for bleeding and thromboembolic complications.</td>
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<td>Weber et al. 2012 (77)</td>
<td>Retrospective cohort analysis, with propensity matching of 103 BP to 103 MP</td>
<td>206 pts undergoing AVR (2000–2009)</td>
<td>Age &lt;60 y. AVR with or without concurrent CABG, aortic root surgery, mitral or additional valve replacement</td>
<td>Median follow-up 33±24 mo (2–120 mo)</td>
<td>Overall survival was worse with BHV (90.3% vs. MHV=98%, p=0.038; HR:0.243, 0.054–0.923) Freedom from valve related complication complications was similar: BHV=54.5% vs. MHV=51.6%, p=NS</td>
</tr>
<tr>
<td>Chang YP et al. 2014 (78)</td>
<td>Retrospective with propensity matching</td>
<td>4,253 pts s/p AVR with MHV or BHV in New York state (1997–2004)</td>
<td>Age &lt;60 y. isolated AVR</td>
<td>Median follow-up time 10.8 y (range, 0 to 16.9 y)</td>
<td>15-y survival: BHV: 60.6% (95% CI: 56.3%-64.9%) MHV: 62.1% (95% CI: 58.2%-66.0%) (HR: 0.97 [95% CI: 0.83-1.14]) 15-y stroke incidence: BHV: 7.7% (95% CI: 5.7%-9.7%); MHV: 8.6% (95% CI: 6.2%-11.0%) HR: 1.04 (95% CI: 0.75-1.43). 15-y reoperation incidence: BHV: 12.1% (95% CI: 8.8%-15.4%); MHV: 6.9% (95% CI: 4.2%-9.6%) HR: 0.52 (95% CI: 0.36-0.75). Bioprostheses were associated with a significantly higher rate of AV reoperation than mechanical prostheses (p=.001) 15-y major bleeding incidence: BHV: 6.6% (95% CI: 4.8%-8.4%); MHV: 13.0% (95% CI: 9.9%-16.1%) HR: 1.75 (95% CI: 1.27-2.43)</td>
</tr>
<tr>
<td>Kaneko T et al. 2014 (79)</td>
<td>Retrospective with propensity matching</td>
<td>768 pts &lt;65 y of age old s/p MVR January 1991 to June 2012</td>
<td>Age &lt;65 s/p MVR</td>
<td>The median follow-up: 7 y MHV: 8 y BHV: 3 y</td>
<td>Long-term survival for propensity matched group: MHV: 13.7+/0.7 y BHV: 11.3+/1.0 y p=0.004 MHV 5-, 10-, and 15-y survival of 83.4%, 69.2%, and 62.6%. BHV 5-, 10-, and 15-y survival of 67.3%, 57.6%, and 40.4% in the MVRb group (p=0.04). Freedom from stroke and embolic events at 5, 10, and 15 y: MHV: 95.3%, 93.2%, and 90.7% BHV: 93.7%, 87.6%, and 87.6%; p=NS after 240 mo Freedom from major bleeding at 5, 10, and 15 y: MHV 87.2%, 79.2%, and 71.2% BHV 91.1%, 85.0%, and 77.9%; p=NS The freedom from reoperation at 5, 10, 15 y: MHV: 97.7%, 96.6%, and 96.1% BHV: 96.6%, 86.6%, and 75.3% The risk of reoperation was significantly greater for the BHV patients (p=.003)</td>
</tr>
</tbody>
</table>
McClure 2014
(80)
1701 pts aged <65 y who underwent AVR between 1992 and 2011. BHV (2nd generation stented), n=769. MHV (bi-leaflet), n=932. Retrospective Stepwise logistic regression propensity score identified subset of 361 evenly matched pairs. 361 matched pairs (Mean age BHV 53.9 y vs. 53.2 y for MHV) "Isolated" stented bioprosthetic or bi-leaflet mechanical AVR. Concomitant root and/or ascending aortic repairs included. Prior cardiac surgery included (1701 of 6794 pts who underwent AVR in this time frame met inclusion criteria). Concomitant valve, coronary or ventricular procedures. Ross procedure Homograft or stentless bioprosthetic AVR. Median follow-up for entire cohort 8 y (1448 pt-y) Median follow-up for matched pairs 6.5 y • For matched cohort: 30-d mortality: 1.9% BHV vs. 1.4% MHV (p=0.77) Survival at 5, 10, 15 and 18 y for BHV vs. MHV: 89% vs. 88%, 78% vs. 79%, 65% vs. 75% and 60% vs 51% (p=0.75). Freedom from reoperation at 18 y: 55% BHV vs. 95% MHV (p=0.002) Freedom from major bleeding 78% MHV vs. 98% BHV (p=0.002). No difference in stroke rates

Du 2014
(81)
Pts >65 y of age in Medicare data base who underwent AVR between July 1, 2006 and December 31, 2011. MHV, n=19190. BHV, n=47263. Retrospective analysis. Mixed-effects model adjusting for physician and hospital random effects to estimate ORs of early mortality for MHV vs BHV. Medicare beneficiaries enrolled in Parts A, B and D for 6 mo before AVR. Age >65 y of age Mean, 77 y of age. 45% of study population underwent concurrent CABG. Medicare Part C beneficiaries. (limited claims data) Up to 365 d after surgery • OR death on d of surgery MHV vs. BHV 1.61 (95% CI: 1.27–2.04; p<0.001); RR: 1.60. NNT: 290. • OR death within 30 d surgery MHV vs. BHV 1.18 (1.09–1.28), p<0.001. NNT 121. • No difference between MHV and BHV d 31–365 after surgery • Consistent findings in subgroup analyses of pts undergoing AVR + CABG but not in subgroup undergoing isolated AVR

Bourguignon 2015A
(82)
2,659 pts who underwent AVR with the CE-Perimount BHV valve (1984-2008) at a single center. Mean age 70.7+/-10.4 y of age (range 16–91 y of age) Age <60 y of age: 383 (13%) Multiple valve replacement Mean followup 6.7+/- 4.8 y (0–24.6 y) Mean followup 6.7+/- 4.8 y (0–24.6 y) • Actuarial survival rates 10 y: 52.4% ± 1.2%; 15 y: 31.1 ± 1.4%; 20 y: 14.4 ± 1.7% Freedom from reoperation from structural valve deterioration: 60 y or less:15 y:70.8% ± 4.1%; 20 y:81.1% ± 5.6%; 60-70 y: 15 y:82.7% ± 2.9%; 20 y: 59.6% ± 7.6% Over 70 y: >15 y:98.1% ± 0.8% Expected valve durability is 19.7 y for the entire cohort.
Bourguignon 2014B
(83)
24667021
450 pts who underwent MVR with the CE-Perimount BHV valve (1984-2011) at a single center
Retrospective, observational
Mean age 68 +/-10.4 y (22-89 y)
Multiple valve replacement
Mean followup 7.2 +/-5.1 y (0-24.8 y)
- 20 actuarial survival rate including early deaths was 16.9% +/-3.9%.
- Valve-related actuarial survival rate was 62.4% +/-9.0%.
- 20 y actuarial freedom from complications was thromboembolism, 83.9% +/-7.6%; hemorrhage, 90.2% +/-10.8%; endocarditis, 94.8% +/-1.4%; structural valve deterioration, 23.7% +/-6.9%; and explanation for structural valve deterioration, 40.5% +/-8.0%.
- The expected valve durability was 16.6 y for the entire cohort (11.4, 16.6, and 19.4 y for pts aged <60, 60 to 70, and >70 y, respectively).

Bourguignon 2015C
(84)
26187006
373 pts <60 y of age underwent AVR with CE-Perimount BHV valve (1984-2008) at a single center
Retrospective, observational
Mean age 51.0 +/-9.2 Median age 54 (47-57.5) Range: 16-60 y
Multiple valve replacement
Mean follow-up was 8.6 +/-5.9 y.
- Actuarial survival rates: 78.1% +/- 2.6%, 65.6% +/- 3.5%, and 46.8% +/- 6.0% after 10, 15, and 20 y
- Actuarial freedom from reoperation rates attributable to structural valve deterioration at 10, 15, and 20 y: 88.3% +/- 2.4%, 70.8% +/- 4.1%, and 38.1% +/- 5.6%

Chikwe, 2015
(85)
25871669
3433 total pts 50-69 y old in New York State who underwent MVR from January 1, 1997, to December 31, 2007. 795 (23.2%) BHV 2638 (76.8%) MHV
Propensity matching: 664 pairs
Retrospective, observational
Mean age: Whole group: 60.1 +/-5.8 BHV: 61.2 +/-5.9 MHV: 59.7 +/-5.7
Out-of-state residency, prior replacement of any valve, concomitant valve replacement, concomitant valve repair, cCABG surgery, or thoracic aortic surgery
Median duration was 8.2 y(range, 0-16.8 y).
- Actuarial 15-y survival in propensity matched group:
  - MHV: 57.5% (95% CI: 50.5-64.4%) BHV: 59.9% (95% CI: 54.8-65.0%) HR:0.95 [95% CI: 0.79–1.15], p=0.62;
  - Stroke 15 y in propensity matched group:
    - MHV: 14.0% (95% CI: 9.5–18.6%) BHV: 6.8% (95% CI: 4.5–8.8%)
    - HR: 1.62 [95% CI: 1.10–2.39], p=0.01
  - Bleeding 15 y in propensity matched group:
    - MHV: 14.9% (95% CI: 11.0–18.7%) BHV: 9.0% (95% CI: 6.4–11.5%)
    - HR: 1.50 [95% CI: 1.05–2.16], p=0.03
  - Reoperation at 15 y in propensity matched group:
    - MHV: 5.0% (95% CI: 3.1–6.9%) BHV:11.1% (95% CI: 7.6–14.6%)
    - HR: 0.59 [95% CI: 0.37–0.94], p=0.03

Retrospective, not randomized, single-center study
Only 1 type of tissue valve used
Pts <60 y of age received BHV if not good candidates for MHV or personal preference
Conflict of interest with

Retrospective, single state in US
15-y follow-up was insufficient to fully assess lifetime risks, particularly of reoperation.
Glaser 2015

4,545 pts 50-69 y old s/p 1° isolated AVR in Sweden from January 1, 1997 to December 31, 2013
MHV: 2713 pts BHV: 1832 pts Propensity matching: 1099 pairs

Retrospective, observational

Mean age (y)
Whole group: 61.4 +/- 5.3
MHV: 59.9 +/- 5.1
BHV: 63.7 +/- 4.7

Prior cardiac surgery or a concomitant procedures
FU for whole group:
Mean: 7.3 +/- 4.7y
Max: 17.2 y
FU for MHV:
Mean 8.8 +/- 4.6y
Max: 17.2 y
FU for BHV:
Mean: 5.0 +/- 3.7 y
Max: 17.2 y

• Greater long-term survival in MHV vs. BHV
• HR: for bioprosthetic vs. mechanical valves
• Overall unadjusted analysis: HR: 1.67; 95% CI: 1.44–1.94
  Overall multivariable adjusted model: HR: 1.30; 95% CI: 1.09–1.56
  Propensity score-matched cohort: HR: 1.34; 95% CI: 1.09 – 1.66; P = 0.006
• Propensity score-matched pts aged 50–59 y: survival greater in MHV: HR: 1.67; 95% CI: 1.06–2.61; p=0.026, n=574).
• Propensity score-matched pts aged 60–69 y: no survival difference in MHV vs. BHV: HR: 1.08; 95% CI: 0.85 – 1.36; p=0.539, n=1502).
• 2° endpoints: Propensity score matched cohort:
  MVH. Stroke: 5.8%; Reoperation: 2.2%; Major bleeding: 9.6%; CV death: 5.2%
  BHV. HR: bioprosthetic vs. mechanical valves
  Stroke: 6.1% HR: 1.04 (95% CI: 0.72–1.50) Reoperation: 5.2% HR: 2.36 95% CI: 1.42–3.94) Major bleeding: 4.9% HR:0.49 (95% CI: 0.34–0.70) CV death: 5.1% HR:1.00 (95% CI: 0.67–1.50)
• 2° endpoints: Overall Cohort:
  MVH. Stroke: 7.6%; Reoperation: 3.1%; Major bleeding: 9.9%; CV death: 5.4%
  BHV. Stroke: 5.1% HR: 0.97 (95% CI: 0.72–1.31) Reoperation: 4.1 % HR: 2.07 (95% CI: 1.38–3.11) Major bleeding: 4.0% HR: 0.53 (95% CI: 0.39–0.74) CV death: 4.0% HR: 1.26 (95% CI: 0.87–1.81).

Isaacs 2015

All pts>18 y old who underwent AVR in NIS database. 767,375 implanted valves

Observational

Median age: 74 y for pts receiving BHV
Median age: 67 y for pts receiving MHV.

Pts who underwent a simultaneous valve annuloplasty, valve repair, or mitral or tricuspid valve replacement were excluded.
All pts aged >18 y in the National Inpatient Sample who received an AVR between 1998 and 2011 were studied

• 767,375 implanted valves. BHV increased from 37.7% in 1998-2001 to 63.6% in 2007-2011.
• Use of bioprosthetic valves increased across all age groups, most markedly in pts age 55 to 64 y.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vincentiis 2008 (88)</td>
<td>345 consecutive pts who underwent AVR from 5/1991-4/2005 at a single institution</td>
<td>Mean age 82±1.2 y (range 80-92)</td>
<td>Retrospective</td>
<td>In hospital mortality: Total group: 7.5% BHV: 8.5% MHV: 6.2% (P=0.536) Late FU: Total group: 61% at 5 y 21% at 10 y 6% at 14 y The NYHA functional class improvement BHV: 3.3 ± 1.2 ± 0.5 (p=0.001) MVH: 3.2 ± 1.2 ± 0.5 Survival by type of prosthesis was significantly higher with mechanical prostheses (log-rank p=0.03). Freedom from cerebrovascular events (thromboembolic/hemorrhagic) at 5 and 10 y: BHV: 92% and 77%; MHV: 89% and 62%</td>
</tr>
<tr>
<td>Vicchio 2008 (89)</td>
<td>160 consecutive octogenarians who underwent AVR at a single institution between July 1992-Sept 2006. BHV: 68 pts MHV: 92 pts 121 pts were alive at follow-up and answered the QoL questionnaire BHV: 62 pts MHV: 98 pts</td>
<td>Mean age of 82.3 ± 2.3 y of age (range, 80 to 90 y of age) BHV: 82.9 ± 12.7 y MHV: 81.8 ± 1.8 y</td>
<td>Retrospective</td>
<td>Total hospital mortality: 8.8% BHV: 10.3%: 7.6% (p=0.75) Survival at 1, 3, 5 and 8 y: BHV: 86.4% +/- 0.4%, 76.9% +/- 0.6%, 58.1% +/- 0.1%, and 46.5% +/- 0.14% MHV: 91.3% +/- 0.03%, 88.6% +/- 0.03%, 81.6% +/- 0.05%, and 70% +/- 0.67% (p=0.025) QOL scores comparable between BHV and MHV</td>
</tr>
<tr>
<td>Dvir D, et al., 2012 (90)</td>
<td>202 pts with degenerated bioprosthetic valves from 38 cardiac centers. Bioprosthesis mode of failure was stenosis (n=85, 42%), regurgitation (n=68, 34%) or combined stenosis and regurgitation (n=49, 24%). Implantated devices: Corevalve: n=124 Edwards: n=78</td>
<td>Mean y of age 77.7 +/- 10.4 All pts in the registry were included</td>
<td>Global valve-in-valve Registry Retrospective collection of data from cases performed before registry initiation, and prospective data collection after that time. Procedural success and 30-d FU One yr FU in 87 pts</td>
<td>Procedural success: 93.1% cases Adverse procedural outcomes: Device malposition: 15.3% Coronary obstruction: 3.5% 30-d FU: All-cause mortality: 8.4% NYHA class III: 83.7% 1 y FU in 87 pts; 85.8% survival</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
<th>Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClure RS, et al. 2014 (80)</td>
<td>Propensity-matched cohort, retrospective single center observational study</td>
<td>n=1,701 pts &lt;65 y referred for isolated AVR (769 received a stented bioprosthetic valve; 932 received a mechanical valve)</td>
<td>Factors associated with 1 yr mortality: Small surgical bioprosthesis (21 mm; HR: 2.04; 95% CI: 1.14–3.67; p=0.02) baseline stenosis (vs. regurgitation; HR: 3.07; 95% CI: 1.33-7.08; p=0.008).</td>
</tr>
<tr>
<td>Repack 2016 (92)</td>
<td>Prospective, observational</td>
<td>N= 146 pts; to assess postoperative QoL in pts with either mechanical or bioprosthetic vales for aortic root repair</td>
<td>Postoperative QoL does not differ for pts receiving mechanical or bioprosthetic valves for aortic root repair.</td>
</tr>
</tbody>
</table>

Potential underestimation of events due to retrospective study design and questionnaire usage.
### Data Supplement 6. Antithrombotic Therapy for Prosthetic Valves (Section 11.2.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| PROACT Puskas J 2014 (93) 24512654  | **Aim:** To assess the efficacy and safety of less intensive anticoagulation (INR 1.5–2.0) in high-risk pts receiving an On-X AVR  
**Study type:** RCT  
**Size:** n=375 pts | **Inclusion criteria:**  
1. Indication for AVR; age ≥ 18 y of age  
2. 1 of the following:  
   a. Chronic AF  
   b. EF <0.30  
   c. LAE (>50 mm)  
   d. LA SEC  
   e. “vascular pathologic features”  
   f. LV or RV aneurysm  
   g. Neurologic events  
   h. Lack of response to ASA or clopidogrel  
   i. Women receiving estrogen  
3. Other cardiac surgery allowed  
   a. CABG  
   b. MV or TV repair  
   c. Ascending aortic replacement  
   d. Maze  
   e. “and so forth”  
**Exclusion criteria:**  
1. R-sided valve replacement  
2. Double valve replacement  
3. Active endocarditis | **Intervention (test group):** Warfarin targeted to INR 1.5–2.0  
**Comparator (control group):** Warfarin targeted to INR 2.0–3.0  
All pts received ASA 81 mg Randomization at 3 mo post-operatively  
All pts were treated with warfarin targeted to INR 2.0–3.0 plus ASA 81 mg daily for first 3 post-operative mo | **1° endpoint:** The 1° endpoints mandated by the FDA included major bleeding events, minor bleeding events, total bleeding events, TIA, hemorrhagic stroke, nonhemorrhagic stroke, any neurologic event, peripheral TE, any TE, valve thrombosis, TE and thrombosis, major event (major bleeding, any TE, valve thrombosis), death (cardiac, noncardiac, valve-related, and all-cause)  
**Safety endpoint (if relevant):** Incorporated in 1° endpoint above  
Selected Results (test vs. control):  
1. Major bleeding rate (%/pt-y): 1.48 vs. 3.31; RR: 0.45; (0.21–0.94, p=0.032)  
2. Total bleeding RR: 0.40 (0.24–0.69) p<0.001  
3. TE + thrombosis RR: 1.60 (0.82–3.17), p=0.178  
3. All events RR: 0.66 (0.44–0.99) p=0.046  
**• Major and minor bleeding events were significantly lower in the INR 2.0–3.0 group vs. the INR 3.0–4.5 group.**  
**• NS difference in thromboembolic event rates in the 2.0–3.0 group compared to the 3.0–4.5 group** | |
| AREVA Acar, et al. 1996 (94) 8901659 | **Aim:** To compare moderate oral anticoagulation (INR 2.0–3.0) to higher intensity anticoagulation (INR 3.0–4.5) following single-MV replacement (Omnicarbon or St. Jude)  
**Study type:** RCT  
**Size:** n=433 pts (380 pts received treatment) | **Inclusion criteria:**  
1. Pts 18–75 y of age, in sinus rhythm, left atrial diameter ≤50 mm  
**Exclusion criteria:** Contraindication to anticoagulant therapy, dialyzed renal failure, hepatic insufficiency, refusal to participate | **Intervention:** INR of 2.0–3.0 (n=188 pts)  
**Comparator:** INR of 3.0–4.5 (n=192 pts) | **1° endpoint:** Thromboembolic, hemorrhagic events, mortality, endocarditis, withdrawal from oral anticoagulant therapy  
**Safety endpoint (if relevant):** None  
**• Major and minor bleeding events were significantly lower in the INR 2.0–3.0 group vs. the INR 3.0–4.5 group.**  
**• NS difference in thromboembolic event rates in the 2.0–3.0 group compared to the 3.0–4.5 group** | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention and Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint (if relevant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hering 2005 (95) 15653962</td>
<td>To compare rates of thromboembolism and anticoagulation after MHV replacement.</td>
<td>Pts undergoing St. Jude Medical AVR, MVR or combined AVR/MVR between July 1993 and May 1999</td>
<td>Group A: INR 3.0–4.5; Group B: INR 2.5–4.0; Group C: INR 2.0–3.5</td>
<td>Incidence of moderate and severe TEs and bleeding complications</td>
<td>None</td>
</tr>
<tr>
<td>Torella, 2010 (96) 20598989</td>
<td>To evaluate the safety of lower intensity oral anticoagulation following isolated mechanical AVR</td>
<td>Pts undergoing St. Jude Medical AVR, MVR or combined AVR/MVR between July 1993 and May 1999</td>
<td>Low-risk pts following bileaflet mechanical AVR</td>
<td>Incidence of moderate and severe TEs and bleeding complications</td>
<td>None</td>
</tr>
<tr>
<td>Mere, 2012 (97) 23188028</td>
<td>To assess the association of warfarin treatment with the risk of thromboembolic complications, bleeding incidents and CV death after bioprosthetic AVR</td>
<td>Pts who had bioprosthetic AVR surgery performed between 1/1/1997 and 12/31/2009</td>
<td>Continued warfarin treatment</td>
<td>Estimated rates of events per 100 person-y in pts not treated with warfarin compared with those treated with warfarin with comparative absolute risk were 7.00 (95% CI: 4.07-12.06) vs. 2.69 (95% CI: 1.49-4.87; adjusted IRR, 2.46; 95% CI: 1.09-5.55) for strokes; 13.07 (95% CI: 8.76-19.50) vs. 3.97 (95% CI: 2.43-6.48; adjusted IRR, 2.93; 95% CI: 1.54-5.55) for thromboembolic events; 11.86 (95% CI: 7.81-18.01) vs. 5.37 (95% CI: 3.54-8.16; adjusted IRR, 2.32; 95% CI: 1.28-4.22) for bleeding incidents; and 31.74 (95% CI: 24.69-40.79) vs. 3.83 (95% CI: 2.35-6.25; adjusted IRR, 7.61; 95% CI: 4.37-13.26) for CV deaths within 30 to 89 d after surgery; and 6.50 (95% CI: 4.67-9.29) vs. 1.50 (95% CI: 0.89-2.53) for CV deaths at least 730 d after surgery</td>
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<td>Group A: INR 3.0–4.5; Group B: INR 2.5–4.0; Group C: INR 2.0–3.5</td>
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<td>Torella, 2010 (96) 20598989</td>
<td>To evaluate the safety of lower intensity oral anticoagulation following isolated mechanical AVR</td>
<td>Pts undergoing St. Jude Medical AVR, MVR or combined AVR/MVR between July 1993 and May 1999</td>
<td>Low-risk pts following bileaflet mechanical AVR</td>
<td>Incidence of moderate and severe TEs and bleeding complications</td>
<td>None</td>
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<tr>
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<td>Pts who had bioprosthetic AVR surgery performed between 1/1/1997 and 12/31/2009</td>
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<td>Estimated rates of events per 100 person-y in pts not treated with warfarin compared with those treated with warfarin with comparative absolute risk were 7.00 (95% CI: 4.07-12.06) vs. 2.69 (95% CI: 1.49-4.87; adjusted IRR, 2.46; 95% CI: 1.09-5.55) for strokes; 13.07 (95% CI: 8.76-19.50) vs. 3.97 (95% CI: 2.43-6.48; adjusted IRR, 2.93; 95% CI: 1.54-5.55) for thromboembolic events; 11.86 (95% CI: 7.81-18.01) vs. 5.37 (95% CI: 3.54-8.16; adjusted IRR, 2.32; 95% CI: 1.28-4.22) for bleeding incidents; and 31.74 (95% CI: 24.69-40.79) vs. 3.83 (95% CI: 2.35-6.25; adjusted IRR, 7.61; 95% CI: 4.37-13.26) for CV deaths within 30 to 89 d after surgery; and 6.50 (95% CI: 4.67-9.29) vs. 1.50 (95% CI: 0.89-2.53) for CV deaths at least 730 d after surgery</td>
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</tr>
</tbody>
</table>

- There was no significant difference in incidence of TEs and bleeding complications among the 3 groups.
- Further study is needed of the intensity of anticoagulants in pts with SJM valve.
- The mean INR was 1.94 ± 0.21 in the Low INR group and 2.61±0.25 in the Conventional INR group (p<0.001)
- No difference in thromboembolic event rates
- Total hemorrhagic events occurred in 6 pts in the low INR group vs. 16 pts in the conventional INR group (p=0.04)
- The low INR is safe and feasible in low risk pts following bileaflet aortic mechanical valve replacement.
### Makkar RR, et al. 2012 (98) 22921973

**Aim:** To investigate the possibility of subclinical leaflet thrombosis in bioprosthetic AVs after TAVR and the effect of anticoagulation

**Study type:** Analysis of 4D volume rendered CT scans from a clinical trial and 2 registries of TAVR

**Inclusion criteria:** Pts who had 4D volume rendered CT scans following TAVR implantation in a clinical trial and 2 registry studies

**Exclusion criteria:** Pts with unusable scans (33 in clinical trial and 8 in registry studies)

**Intervention and Comparator:**
- Group A: Initiated or continued anticoagulation
- Group B: No anticoagulation

**Results:** Reduced leaflet motion was noted on CT in 22 of 55 pts (40%) in the clinical trial and 17 of 132 pts (13%) in the 2 registries. Reduced leaflet motion was detected among pts with multiple bioprostheses types, including transcatheter and surgical bioprostheses. Therapeutic anticoagulation with warfarin, as compared with DAPT, was associated with a decreased incidence of reduced leaflet motion (0% and 55%, respectively, p=0.01 in the clinical trial; and 0% and 29%, respectively, p=0.04 in the pooled registries). In pts reevaluated with follow-up CT, the condition resolved with therapeutic anticoagulation.

### Egbe AC, et al. 2015 (99) 26610876

**Aim:** To determine the diagnostic features of BPVT

**Study type:** Pathology database analysis

**Size:** n=46 pts

**Inclusion criteria:** 46 of 397 consecutive cases of explanted bioprosthesis in the Mayo Clinic pathology database between 1997–2013 which were diagnosed as BPVT, matched 1:2 for age, sex and bioprosthesis position with pts whose valves were explanted for structural failure

**Exclusion criteria:** Pts whose valves were explanted for structural failure

**Intervention and Comparator:** BPVT vs. structural deterioration of bioprosthesis

**Results:** 46 cases of BPVT (11.6%; aortic 29, mitral 9, tricuspid 7, pulmonary 1), mean age 63 y, and 68% were male. 30 (65%) cases occurred >12 mo post-implantation; median bioprosthetic valve longevity was 24 mo (cases) vs. 108 mo (controls) (p<0.001). Independent predictors of BPVT were >50% increase in mean echo-Doppler gradient from baseline within 5 y (OR: 12.7), paroxysmal AF (OR: 5.19), subtherapeutic INR (OR: 7.37), increased cusp thickness (OR: 12.2), and abnormal cusp mobility (OR: 6.94). Presence of all 5 diagnostic features was predictive of BPVT with 76% sensitivity, 93% specificity, 85% positive predictive value, and 89% negative predictive value (p<0.001).

### Brennan et al. 2012 (98) 22921973

**Aim:** To evaluate the risks and benefits of short-term anticoagulation in pts receiving an aortic valve bioprosthesis

**Study type:** STS Adult Cardiac Database analysis

**Size:** n=25,656

**Inclusion criteria:** Pts >65 y who had bioprosthetic AVR surgery performed between 2004–2006

**Exclusion criteria:** Pts in whom clinical equipoise for anticoagulation was unlikely, including those with preoperative indication for warfarin, an indwelling mechanical valve, a predischarge contraindication to warfarin, a complication related to anticoagulation or those who died before hospital discharge

**Intervention and Comparator:**
- Group A: ASA only
- Group B: ASA and warfarin
- Group C: Warfarin only

**1st endpoint:** Death, repeat hospitalization for embolic events or bleeding

Among those receiving ASA-only, 3-mo adverse events were low (death, 3.0%; embolic events, 1.0%; bleeding events, 1.0%). Relative to ASA-only, those treated with warfarin plus ASA had a lower adjusted risk of death (RR: 0.80; 95% CI: 0.66–0.96) and embolic event (RR: 0.52–0.75) but a higher risk of bleeding (RR: 2.80; 95% CI: 2.18–3.60). Relative to ASA-only, warfarin-only pts had a similar risk of death (RR: 1.01; 95% CI: 0.80–1.27), embolic events (RR: 0.95; 95% CI: 0.61–1.47), and bleeding (RR: 1.23; 95% CI: 0.85–1.79).

**2nd endpoint:** Death and embolic events were relatively rare in the first 3 mo after bioprosthetic AVR

Compared with ASA-only, ASA plus warfarin was associated with a reduced risk of death and embolic events, but at the cost of an increased bleeding risk.

**Death and embolic events were relatively rare in the first 3 mo after bioprosthetic AVR**

**Compared with ASA-only, ASA plus warfarin was associated with a reduced risk of death and embolic events, but at the cost of an increased bleeding risk.**

**BPVT is not uncommon and can occur several years after surgery.**

**A combination of clinical and echocardiographic features can reliably diagnose BPVT**
### Hansson NC et al. 2016 (101) 27580689

**Aim:** To assess the incidence, potential predictors, and clinical implications of THV thrombosis as determined by contrast-enhanced MDCT after TAVR  

**Study type:** Analysis of contrast enhanced MDCT scans from consecutive pts undergoing TAVR  

**Size:** n=405 pts  

**Inclusion criteria:** 460 consecutive pts who underwent TAVR at a single center between 2011-2016  
**Exclusion criteria:** 55 pts who did not have contrast enhanced MDCT scans at 1-3 mo following TAVR  

**Intervention and Comparator:**  
- **Group A:** Treatment with warfarin  
- **Group B:** No treatment with warfarin  

**Results:** MDCT verified THV thrombosis in 28 of 405 (7%) pts. A total of 23 pts had subclinical THV thrombosis, whereas 5 (18%) pts experienced clinically overt obstructive THV thrombosis. The risk of THV thrombosis in pts who did not receive warfarin was higher compared with pts who received warfarin (10.7% vs. 1.8%; RR: 6.09; 95% CI: 1.86–19.84). A larger THV was associated with an increased risk of THV thrombosis (p=0.03). In multivariable analysis, a 29-mm THV (RR: 2.89; 95% CI: 1.44–5.80) and no post-TAVR warfarin treatment (RR: 5.46; 95% CI: 1.68–17.7) independently predicted THV thrombosis. Treatment with warfarin effectively reverted THV thrombosis and normalized THV function in 85% of pts as documented by follow-up TEE and MDCT.  

- Incidence of THV thrombosis in this large study was 7%.  
- A larger THV size may predispose to THV thrombosis, whereas treatment with warfarin appears to have a protective effect.

### Pache et al. 2016 (102) 26446193

**Aim:** To evaluate the frequency of early hypo-attenuated leaflet thickening of transcatheter AVs  

**Study type:** Analysis of ECG gated dual source CTA angiography following TAVR at median of 5 d after implantation  

**Size:** n=156 pts  

**Inclusion criteria:** 249 pts who had TAVR at a single institution between 2014-2015  
**Exclusion criteria:** Pts who had a contraindication for CTA due to acute renal failure, impaired renal function, missing consent, or inability to undergo a CTA examination (93 pts)  

**Intervention and Comparator:**  
- **Group A:** Presence of hypo-attenuated leaflet thickening  
- **Group B:** Absence of hypo-attenuated leaflet thickening  

**Results:** Hypo-attenuated leaflet thickening was found in 16 pts [10.3% (95% CI: 5.5%–15.0%)]. Hypo-attenuated leaflet thickening was not associated with clinical symptoms, but a small, albeit significant difference in mean pressure gradient at the time of CTA (11.6 ± 3.4 vs. 14.9 ± 5.3 mm Hg, p=0.026). Full anticoagulation led to almost complete resolution of hypo-attenuated leaflet thickening in 13 pts with follow-up CTA.  

- Hypo-attenuated leaflet thickening occurred in 10% of pts undergoing TAVR  
- Early hypo-attenuated leaflet thickening is clinically inapparent and reversible by full anticoagulation.
### Data Supplement 21. *(Updated From 2014 Guideline)* Bridging Anticoagulation Therapy for Mechanical Heart Valves (Section 11.3.2)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Study Size and Comparator (N)</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammerstingl C, et al. 2007 (103) 17578050</td>
<td>Prospective, observational</td>
<td>Pts with MHV undergoing major surgery (n=25) or minor surgery (n=56), pacemaker implantation (n=21), or cardiac cath (n=34)</td>
<td>N/A</td>
<td>No thromboembolic (95% CI: 0–3.1%) complications. 1 major bleeding complication (0.86%; 95% CI: 0.02–4.7%). Minor bleeding in 10 pts (8.6%; 95% CI: 4.2–15.3%) at a mean of 5.4±1.4 d LMWH therapy.</td>
<td>Not randomized, no comparison group, relatively small study group.</td>
</tr>
<tr>
<td>Spyropoulos, et al. 2008 (104) 18805116</td>
<td>Observational, prospective, multicenter registry in USA, Canada</td>
<td>Adults undergoing elective surgery or invasive procedure with a mechanical valve on long-term VKA</td>
<td>Enrolled in another bridging study within 30 d. 73 with IV UFH (1,53±532 U/h) vs. 172 with SQ LMWH (76% enoxaparin 1 mg/kg bid, 13% dalteparin 100 U/kg bid, 4% tinzaparin 175 U/kg/d)</td>
<td>Major adverse event rates (5.5% vs. 10.3%; P=0.23) and major bleeds (4.2% vs. 8.8%; P=0.17) were similar in the LMWH and UFH groups, respectively; 1 arterial thromboembolic event occurred in each group. More LMWH-bridged pts were treated as out pts or discharged from the hospital in &lt;24 h (68.6% vs. 6.8%; P &lt;0.0001). Multivariate logistic analysis found no significant differences in major bleeds and major composite adverse events when compared to UFH.</td>
<td>Not randomized, bridging therapy chosen by clinician. The LMWH group was less likely to undergo major surgery (33.7% vs. 58.9%; P=0.0002) and cardiothoracic surgery (7.6% vs. 19.2%; P=0.008), and to receive intraprocedural anticoagulants or thrombolytics (4.1% vs. 13.7%; P=0.007)</td>
</tr>
<tr>
<td>Pengo, et al. 2009 (105) 19470892</td>
<td>Prospective inception cohort at 22 Italian centers, 2005–2007</td>
<td>Adults undergoing surgical or invasive procedures that required interruption of long-term VKA therapy</td>
<td>Body weight &lt;40 kg. Creatinine &gt;2.0 mg/dL, contraindication to LMWH, need for dual antiplatelet Rx</td>
<td>N=189 MHV valve pts (15% of total study size of 1,262). Bridging with 70 anti-Xa U/kg bid for high-risk pts.</td>
<td>Only 15% had mechanical valves, no comparison group. Safety in pts with MHV valves has not been conclusively established</td>
</tr>
</tbody>
</table>

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UFH or LMWH bridging used in high-risk pts (older AVR, any MVR, additional risk factors for TE). No bridging in isolated AVR pts.

Minor Bleeding
Overall cumulative incidence of TE at 3 mo was 0.9%; all 1 wk of the procedure. No TE events in pts with no bridging events occurred within in 53 pts with isolated A VR, 13 (6.1) 13 (5.4) 8 (8.1)

Bui HT, et al. 2009 (107) 19892063
Retrospective cohort study 173 pts on VKA anticoagulation for MHV (n=90) or for nonvalvular AF undergoing invasive or surgical procedures Age <18 y, Pregnancy, Hypercoagulable condition, bioprosthesis valve 130 bridging episodes with LMWH were used to compare outcomes in MHV vs. pts with AF. No deaths or thromboembolic events at 2 mo. Major and minor bleeding rates were similar between the MHV and AF groups (3.2% and 2.9%, 14.5% and 13.2% respectively, p=NS).

Bleeker, et al. 2012 (108) 22591673
Prospective cohort, single-center Consecutive pts undergoing noncardiac surgery Bioprosthetic valves, severe liver or renal disease, contraindication to heparin 140 pts with MHV (77 AVR, 46 MVR, and 17 DVR) receiving enoxaparin 1 mg/kg bid compared to 1,200 pts with native valves (control group) receiving no anticoagulation. Not randomized. Comparative group did not have valve disease. No power calculation with small number of MHV pts.

Weiss, et al. 2013 (109) 23648452
Retrospective, single-center cohort study Consecutive pts requiring postoperative bridging therapy after cardiac surgery during a 19 mo period N/A N=402 receiving LMWH (enoxaparin): comparison of full-dose (FD=1 mg/kg bodyweight bid) to half-dose (HD=0.5 mg/kg bid) with renal function dose adjustment. Not randomized, but well matched (first half of cohort received FD, second half HD) included only 100 (25.9% of total) pts with MHV, also included AF in 83.6%.
Douketis, et al. 2015 (110) 26095867
RCT, double-blind, placebo-controlled trial
Pts with chronic AF or flutter receiving warfarin therapy for at least 3 mo undergoing elective surgery
Mechanical heart valve, at least 1 CHADS2 risk factor cardiac, intracranial or intraspinal surgery.
N=1884; 950 with no bridging therapy. 934 assigned to bridging with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 d before the procedure until 24 h before the procedure and then for 5 to 10 d after the procedure.
The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% CI: −0.6 to 0.8; p=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (RR: 0.41; 95% CI: 0.20-0.78; p=0.005 for superiority).
Population excluded pts with MHV and was predominantly low risk for thromboembolism.

Pengo, et al. 2007 (111) 17636186
Randomized, prospective, multicenter, pilot study
Inclusion: Consecutive pts having AVR and/or MV replacement with MHVs for the first time.
Exclusion: Need for adjunctive antiplatelet therapy, ASA allergy/ intolerance; combined CABG, emergency surgery, follow-up problems, poor compliance, renal or hepatic insufficiency, life expectancy <12 mo
Pts randomized to 2 groups; Group A (n=94): receiving low-intensity VKA treatment (target INR 2.5) [plus ASA (100 mg/d) for the first 6 mo]; Group B (n=104): receiving standard-intensity (moderate to high) VKA treatment (target INR 3.7).
1° outcomes:
• Systemic embolism/thromboembolic complications
• Major bleeding/bleeding complications
• Vascular death
Cumulative 1° outcome incidence:
GROUP A - 5.8% (95% CI: 0.9–10.7)
GROUP B – 4.3% (95% CI: 0.2–8.4), p=0.6
Low-intensity VKA plus ASA for first 6 mo appears as effective and safe as standard-intensity VKA.
Pts: • Received subcutaneous unfractionated heparin for 2 consecutive d until INR >2.0 • Stratified by: aortic, mitral, double valve replacement • Randomized to Group A or B at first warfarin administration in blocks of 10 • In addition to warfarin, Group B pts received 100 mg ASA from operation to 6 mo.
Analysis: • Large trial should involve sample size of 350 pts in each group.

Data Supplement 7. Prosthetic Valve Thrombosis (Section 11.6)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) &amp; Study Comparator (# patients)</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keuleers S, et al. 2011 (112) 21211605</td>
<td>Aim: to review the outcome of TT vs surgery for obstructive PVT Study type: Single-center retrospective study Size: n=30 pts with mechanical PVT (1 bioprosthesis)</td>
<td>Inclusion criteria: prosthetic valve dysfunction with thrombus present Exclusion criteria: Patient Population: 81% women, mean age 59, NYHA Class IV 42%, all mitral</td>
<td>Intervention: tPA 10 mg then 90 mg over 2 h (13 pts) Comparator: surgery (18 pts)</td>
<td>1° endpoint: Complete clinical response = complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication Results: Complete clinical response 62% partial response in 31% in obstructive. Size of thrombus not related to outcome. Complications: 2 deaths at surgery, recurrence 31% in TT group with 1 death, other TT complications 1 CVA 1</td>
<td>• Conclusion: TT can be given to pts with PVT with outcomes similar to standard surgical therapy • Limitation: single-center study with small number of pts and no standardized approach to treatment • Comments: Authors felt TT is an attractive first line therapy for PVT</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
</tr>
<tr>
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</tr>
<tr>
<td>Nagy A et al. 2009 (113) 19557981</td>
<td>to assess effect of thrombus size, severity of symptoms and type of valve on success and complication rate of TT for PVT</td>
<td>obstructive – restricted leaflet motion with increased gradient, non-obstructive – thrombus on TEE</td>
<td>bolus and continuous infusion of SK, UK up to 72 h</td>
<td>N/A</td>
<td>complete clinical response = complete</td>
</tr>
<tr>
<td>Size</td>
<td>n=62 episodes in 55 pts identified by TEE</td>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td>hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication</td>
</tr>
<tr>
<td>Study type</td>
<td>Single-center retrospective study</td>
<td>Patient Population:</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61% women, mean age 56, NYHA Class III/IV</td>
<td>SK or UK load with continuous infusion until successful) as initial therapy in 30 mitral and 2 aortic obstructive, surgery in 9 mitral and 1 aortic, Nonobstructive-heparin first</td>
<td>NA</td>
<td>complete clinical response 73% partial response in 21% in obstructive. Size of thrombus not related to outcome.</td>
</tr>
<tr>
<td>Size</td>
<td>9% with TT – heparin ineffective with both obstructive and non-obstructive.  Average thrombus area 1.06 cm2 obstructive and 0.59 cm2 in nonobstructive</td>
<td>Patient Population:</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td>Lengyel M et al. 2001 (114) 11603604</td>
<td>to compare the efficacy and safety of heparin vs TT vs surgery in pts with both obstructive and nonobstructive PVT</td>
<td>obstructive – restricted leaflet motion with increased gradient, nonobstructive – thrombus on TEE</td>
<td>Obstructive – heparin or TT (SK or UK load with continuous infusion until successful) as initial therapy in 30 mitral and 2 aortic obstructive, surgery in 9 mitral and 1 aortic, Nonobstructive-heparin first</td>
<td>NA</td>
<td>complete clinical response = complete</td>
</tr>
<tr>
<td>Study type</td>
<td>Single-center retrospective study</td>
<td>Exclusion criteria: recurrent PVT or contraindication to TT</td>
<td></td>
<td></td>
<td>hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient Population:</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58% women, mean age 53, NYHA Class III/IV</td>
<td>Obstructive – heparin or TT (SK or UK load with continuous infusion until successful) as initial therapy in 30 mitral and 2 aortic obstructive, surgery in 9 mitral and 1 aortic, Nonobstructive-heparin first</td>
<td>NA</td>
<td>complete clinical response 86% partial response in 9% with TT – heparin ineffective with both obstructive and no obstruction with half leading to obstruction</td>
</tr>
<tr>
<td>Size</td>
<td>85 episodes in 59 pts identified by TEE</td>
<td>Exclusion criteria: thrombus on TEE, increased gradient, non-obstructive</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td>Karthikeyan G et al. 2009 (115) 19738134</td>
<td>to compare the efficacy and safety of an accelerated infusion vs conventional infusion of SK in pts with PVT</td>
<td>obstructive – restricted leaflet motion with increased gradient, nonobstructive – thrombus on TEE</td>
<td>accelerated 1.5 million units (MU) SK bolus followed by 1 MU/h vs .25 MU bolus followed by 1 MU/h up to 96 h</td>
<td>N/A</td>
<td>complete clinical response = complete</td>
</tr>
<tr>
<td>Study type</td>
<td>Randomized controlled prospective trial</td>
<td>Exclusion criteria: recurrent PVT or contraindication to TT</td>
<td></td>
<td></td>
<td>hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient Population:</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44% women, mean age 33, NYHA Class III/IV</td>
<td>accelerated 1.5 million units (MU) SK bolus followed by 1 MU/h vs .25 MU bolus followed by 1 MU/h up to 96 h</td>
<td>NA</td>
<td>complete clinical response 58%, complete hemodynamic response 63%. No difference in the 2 infusions in terms of response or complications</td>
</tr>
<tr>
<td>Size</td>
<td>120 pts entered into randomization for PVT</td>
<td>Exclusion criteria:</td>
<td>intervention:</td>
<td>Comparator:</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>first episode of left sided PVT (immobile or hypomobile leaflets on fluoroscopy)</td>
<td>accelerated 1.5 million units (MU) SK bolus followed by 1 MU/h vs .25 MU bolus followed by 1 MU/h up to 96 h</td>
<td>N/A</td>
<td>complete clinical response = complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td>hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recurrent PVT or contraindication to TT</td>
<td></td>
<td></td>
<td>results of high mortality with surgery (29%) to mortality with TT (6%) as sicker pts in the surgery group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient Population:</td>
<td></td>
<td></td>
<td>heparin alone inadequate in 82%, Authors state that TT is treatment of choice for all pts with PVT.</td>
</tr>
</tbody>
</table>

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Caceres-Loriga et al 2006 (116) 16622616

**Aim:** To determine the efficacy and safety of TT for PVT

**Study type:** Single-center retrospective review

**Size:** 69 consecutive pts with PVT

**Inclusion criteria:** Consecutive pts presenting with left sided obstructive PVT and no contraindication to TT

**Exclusion criteria:** 2 pts with a contraindication to TT

**Patient Population:** 78% women, mean age 42 y, NYHA Class III/IV 94%, valve type (mitral 50, aortic 9, tricuspid 9) all obstructive

**Intervention:** Bolus and continuous infusion of SK up to 72 h

**Comparator:** N/A

1° endpoint: complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy)

**Results:** complete hemodynamic response 80.6%, partial response 8.3%, no response 11%

**Complications:** 4 deaths, 5 embolic complications (3 CVA and 5 TIA), 3 major hemorrhage (2 intracranial bleeding). 16% had recurrence in follow-up

**Conclusion:** TT is effective in 80% of pts but with a high rate of embolism, Recurrence rate is high.

**Limitation:** Single-center retrospective study

**Comments:** Authors recommended TT as first line of therapy in all pts

Gupta et al 2000 (117) 11099995

**Aim:** To determine the short and long-term results of TT for PVT

**Study type:** Single-center retrospective review

**Size:** n=110 consecutive pts with obstructive PVT

**Inclusion criteria:** All pts presenting with left sided obstructive PVT and no contraindication to TT

**Exclusion criteria:** 6 pts with contraindication to thrombolysis

**Patient Population:** 53% women, mean age 68, NYHA Class III/IV 80%, valve type (mitral 96, aortic 14), all obstructive

**Intervention:** Bolus and continuous infusion of SK up to 72 h

**Comparator:** N/A

1° endpoint: Complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy)

**Results:** Complete hemodynamic response 81.8%, partial response 10%, and no response 8.2%. 23% had recurrence in follow up.

**Complications:** 8 deaths, 21 embolic complications (6 CVA and 5 TIA), 9 major hemorrhage (5 intracranial bleeding)

**Conclusion:** TT is effective in 80% of pts but with a high rate of embolism, particularly if in AF. Recurrence rate is high.

**Limitation:** Single-center study with 10% lost to follow-up. TEE was not done in majority.

**Comments:** pts who died were primarily those with severe Class IV HF and 3 died within 2 h of infusion (not enough time for TT to work), of incomplete responders only 3/11 did well

Roudaut et al 2009 (118) 19427604

**Aim:** To define the efficacy and safety of thrombolysis vs surgery for PVT

**Study type:** Single-center retrospective review

**Size:** n=210 pts; treated by TT (n=127 pts) or surgery (n=136 pts)

**Inclusion criteria:** All pts at single institution treated for PVT

**Exclusion criteria:** None

**Patient Population:** 66% women, mean age 59, NYHA Class III/IV 66%, valve type (mitral 169, aortic 84, tricuspid 4), obstructive/nonobstructive 148/25

**Intervention:** SK (49), UK (41), rTPA (37), combination (38)

**Comparator:** surgery with either valve replacement (106) or declotting pannus excision (30)

1° endpoint: Hemodynamic success (complete normalization of hemodynamics by echo and fluoroscopy)

**Results:** Hemodynamic success higher in surgery 89% vs TT group 71%

**Complications:** Mortality similar (10%) both groups, total complications (25% vs 11%) and embolic events (15% vs 0.7%) higher in TT vs surgery group

**Conclusion:** Surgery had a higher success rate and lower complication rate than TT

**Limitation:** Single-center experience which changed over time – surgery the more preferred therapy with time

**Comments:** NYHA class at presentation was strongest predictor of late death. Long-term follow-up at 6 y=– better outcome in terms of mortality and recurrence with surgery 76% of pts were subtherapeutic on their INR before presentation, 23% had temporary cessation of warfarin
Ozkum M et al, 2013

**Aim:** To determine whether thrombus size can predict outcome of thrombolysis therapy for PVT.

**Study type:** Registry of TEE performed prior to TT for PVT

**Size:** n=107 pts entered into registry

**Inclusion criteria:** Pts suspected of PVT obstruction or thrombus formation undergoing TEE prior to TT

**Exclusion criteria:**
- Patient Population: 107 pts from 14 centers, 71% women, mean age 43, 41% NYHA Class III/IV, valve type (84% mitral, 19 aortic, 13 tricuspid), NYHA Class III-IV 63%, 99 obstructive vs 14 nonobstructive

**Intervention:** Slow infusion SK (54%), UK (17%) or tPA (29%)

**Comparator:** N/A

**1° endpoint:** Complete hemodynamic success (hemodynamics to normal range), partial hemodynamic success (partial improvement in hemodynamics), clinical success (hemodynamic success without complication)

**Results:** Complete hemodynamic success 76%, partial hemodynamic success 8.6%, clinical success 74%

**Complications:** Overall complications in 17.8%. Death 5.6%, left sided embolic rate 14%, major complication of death, CVA, MI, cerebral bleed in 9.3%

**Conclusion:** Thrombus area >0.8cm², Hx of stroke and NYHA Class III/IV was predictive of complications and poor outcome

**Limitation:** Registry study from 14 centers with strict inclusion criteria and differing thrombolytic regimens – a study more of the TEE predictors rather than outcome of thrombolysis

**Comments:** Soft mass increased success to 91% but still 75% success without soft mass

Thrombus size was an important predictor of complication even in Class III/IV pts

---

TROIA Trial.
Ozkan M, et al 2013

**Aim:** To identify the most effective and safest TEE-guided thrombolytic regimen for PVT.

**Study type:** Single-center, non-randomized, prospective

**Size:** 182 consecutive pts with 220 episodes of PVT

**Inclusion criteria:** Pts with obstructive PVT, nonobstructive PVT with recent thromboembolism, or a thrombus diameter of ≥10 mm

**Exclusion criteria:** Contraindication to TT, nonobstructive PVT with a thrombus diameter of <10 mm and no recent thromboembolism, prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion

**Patient population:** 182 pts, 71% female, mean age 43, 41% NYHA Class III/IV, valve type (84% mitral, 10% aortic), 48% obstructive, 52% nonobstructive

**Intervention:** Different thrombolysis regimens:
- Group I: Rapid streptokinase (16)
- Group II: Slow streptokinase (41)
- Group III: High dose tPA (12)
- Group IV: Half dose, bolus and slow tPA infusion (27)
- Group V: low dose, non –bolus and slow tPA infusion (124)

**Comparator:** N/A

**1° endpoint:** Thrombolytic success
- Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3)
- Nonobstructive: >75% reduction thrombus size

**Results:** Successful thrombolysis in 83.2% of cases (68.8%, 85.4%, 75.0%, 81.5%, 85.5% respectively; p<0.46)

**Complications:** Overall complication rate of 18.6%. Lower combined complication rate in Group V (10.5%) vs. other groups (24%-39%)

Absence of mortality in Group V. The predictors of combined mortality plus nonfatal major complications were any TT regimen other than Group V (OR group 1 through IV: 8.2, 3.8, 8.1 and 4.1 respectively, p<0.05 for each)

**Conclusion:** Low-dose nonbolus slow tPA infusion resulted in the highest success rate of thrombolysis and lowest combined complication rate.

**Limitation:** Single-center nonrandomized study with small number of pts in each group, included both obstructive and nonobstructive PVT

**Comments:** 64 pts who had a contraindication to thrombolysis or failed thrombolysis underwent surgery with a 27% mortality

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Ozkum M et al, 2013

**Aim:** To evaluate the safety and efficacy of low-dose, slow infusion tPA activator for the treatment of PVT in pregnant women

**Inclusion criteria:** Pregnant pts. with obstructive and nonobstructive PVT with recent thromboembolism and thrombus diameter of >5mm and pts with asymptomatic mobile nonobstructive PVT with thrombus

**Intervention:** Low dose tPA – 25 mg over 6 h, repeat at 24 h

**Comparator:** N/A

**1° endpoint:** Thrombolytic success
- Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3)
- Nonobstructive: >75% reduction thrombus size

**Result:** 100% thrombolytic success. (Obstructive PVT group thrombus area, mean, 1.7±1.2 cm²; range, 0.8–6

**Conclusion:** Low dose slow infusion of tPA is an effective and safe regimen for PVT in pregnant women

**Limitation:** Single-center nonrandomized trial with small number of pts.; included both obstructive and nonobstructive PVT
Study type: Single-center, nonrandomized, prospective (subgroup of TROIA trial)

Size: 24 consecutive pregnant pts with 28 episodes of PVT (all mitral – 23 mechanical)

diameter of ≥10 mm

Exclusion criteria: Pts. with contraindication to TT, asymptomatic non obstructive PVT with a thrombus diameter of <10mm and no recent thromboembolism, pts with imminent abortion or placenta previa, pts with prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion

Patient population: 24 women during 25 pregnancies and 28 episodes PVT, mean age 29, mean gestational age 19 wk, NYHA class III/IV (50%) obstructive in 15 (all mitral), nonobstructive in 13

Patient population: 24 women during 25 pregnancies and 28 episodes PVT, mean age 29, mean gestational age 19 wk, NYHA class III/IV (50%) obstructive in 15 (all mitral), nonobstructive in 13

cm²; nonobstructive PVT group, mean, 0.9±0.4 cm²; range, 0.4-1.8 cm²; p=0.022 . No remaining thrombus after TT on TEE)

Complications: no complications in the mother, 20 live births with 1 placental hemorrhage and 1 minor bleeding, 20% miscarriages

Comment: this is a subset of the Ozkun 2013 series.

PORMETEE Trial

Aim: To identify the efficacy and safety of TEE-guided ultraslow infusion of low-dose tPA for PVT.

Study type: Single-center, nonrandomized, prospective

Size: 114 consecutive pts with 120 episodes of PVT (113 mechanical PVT)

Inclusion criteria: Pts with obstructive PVT, nonobstructive PVT with recent thromboembolism, or a thrombus diameter of ≥10 mm

Exclusion criteria: Contraindication to TT, nonobstructive PVT with a thrombus diameter of <10 mm and no recent thromboembolism, Prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion

Patient Population: 65% female, mean age 49, NYHA Class III/IV (35%), obstructive in 77 (23 aortic, 40 mitral 4 tricuspid, 2 double valve), nonobstructive in 43 (10

Intervention: Low dose tPA – 25 mg over 6 h, repeat every 24 h

Comparator: N/A

1st endpoint: Thrombolytic success
Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3)
Nonobstructive: >75% reduction thrombus size

Result: Successful thrombolysis in 90%. Only independent predictor of unsuccessful result was higher NYHA Class.

Complications: Total complications in 8 pts (6.7%) – death (0.8%), major complication (3.3%), minor complication (2.5%). – 1 stroke, 1 peripheral embolism and 4 hemorrhage

Conclusion: Low dose nonbolus slow tPA infusion resulted in the high success rate of thrombolysis (90%) and low combined complication rate (embolism 1.7%, major bleed 1.7% minor bleed 1.7%)

Limitation: single-center nonrandomized study with small number of pts, included both obstructive and nonobstructive PVT. Only 4 pts were in NYHA Class IV

Comments: success rate 20% after first dose and required up to 8 doses, Median number sessions >2, median dose tPA = 64 mg
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st Endpoint</th>
<th>Results</th>
<th>Safety Endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational</td>
<td>To determine the clinical and echocardiographic parameters to differentiate thrombus from pannus formation for obstructed mechanical prostheses</td>
<td>23 pts with 24 obstructed mechanical prostheses (surgical confirmation)</td>
<td>14 pts thrombus</td>
<td>10 pts pannus</td>
<td>Thrombus vs. pannus</td>
<td>Pts with thrombus: shorter duration of symptoms, lower rate of anticoagulation. TEE soft mass: 92% of thrombus, 29% of pannus.</td>
<td>Duration of symptoms and anticoagulation status and ultrasound intensity of mass can differentiate pannus from thrombus.</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>To determine the utility of MDCT to differentiate thrombus from pannus formation for obstructed mechanical prostheses</td>
<td>62 pts with mechanical prosthesis (thrombolysis success or surgical confirmation)</td>
<td>N/A</td>
<td>N/A</td>
<td>Definitive dx 37 pts: 22 thrombus and 17 pannus.</td>
<td>Attenuation value of Hounsfield Units (HU) differentiated thrombus from pannus: HU &gt;145 units for differentiating thrombus from pannus. 87% sensitivity, 95% specificity.</td>
<td>64 slice MDCT is helpful in differentiating pannus from thrombus in pts with mechanical prosthetic obstruction.</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>To determine the benefit of cine-flouroscopy for mechanical prosthetic valve dysfunction</td>
<td>229 pts with mechanical valve prosthesis underwent Doppler echocardiography and fluoroscopy. n=221 prosthetic valves for analysis</td>
<td>N/A</td>
<td>N/A</td>
<td>Flouroscopy identified 87 single leaflet and 134 bileaflet prostheses.</td>
<td>Disk motion differentiated between normal and abnormal prosthetic function by opening angle: Normal 74 +/- 13 degree, Abnl 49 +/- 18 degree.</td>
<td>Flouroscopy is superior to echo in identifying disc motion, while Doppler allows measurement of gradient.</td>
<td></td>
</tr>
<tr>
<td>Observational; to evaluate the diagnostic efficacy of cine-flouroscopy, TTE and TEE</td>
<td>consecutive pts with mechanical valves and suspected valve thrombosis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>TEE is not required in Gp A. TEE showed thrombus in 33% of Gp B. TEE ruled out thrombus in Gp C.</td>
<td>TEE is the gold standard for dx of prosthetic valve thrombosis when either fluoroscopy and TTE are nondiagnostic.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| Barbetseas, et al. 1998 (123) 9809956 | aortic, 26 mitral, 7 double valve | | | | | | |
| Gunduz, et al. 2015 (124) 26659372 | | | | | | | |
| Cianciulli, et al. 2005 (125) 16245506 | | | | | | | |
| Montorsi, et al. 2000 (126) 11078238 | | | | | | | |</p>
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muratori, et al. 2006 (127) 16377291</td>
<td>Pts with mechanical prosthesis for cardioversion or suspected valve dysfunction</td>
<td>N/A</td>
<td>N/A</td>
<td>Mitral prosthesis: 18 single disk 48 bileaflet Aortic prosthesis: 22 single disk 23 bileaflet</td>
<td>TEE is accurate for leaflet motion with MVR and but not for AVR</td>
</tr>
<tr>
<td>Inclusion criteria: Pts with mechanical prosthesis for cardioversion or suspected valve dysfunction</td>
<td>N/A</td>
<td>N/A</td>
<td>Mitral prosthesis: TEE 85% Aortic prosthesis: TEE 100%</td>
<td>TEE showed thrombus in 14% of Gp D</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>N/A</td>
<td>N/A</td>
<td>Mitral prosthesis: TEE 13% Aortic prosthesis: TEE 35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suy, et al. 2016 (128) 27096962</td>
<td>Pts who underwent repeat AVR due to valve dysfunction</td>
<td>N/A</td>
<td>N/A</td>
<td>CT feasible in 23 pts.</td>
<td>CT was additive to TEE in determination of mechanical valve dysfunction</td>
</tr>
<tr>
<td>Inclusion criteria: Pts with prosthetic valves in whom obstruction was suspected but no cause found</td>
<td>N/A</td>
<td>N/A</td>
<td>CT identified morphologic etiology of obstruction in 8 of 13 pts, confirmed at surgery in 6 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Findings by CT: Sub-prosthetic substrate – 8 pts Leaflet motion restriction - 7 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symersky P, et al 2009 (129) 19801036</td>
<td>Pts with prosthetic valves</td>
<td>N/A</td>
<td>N/A</td>
<td>Multidetector CT scan can identify causes of abnormal prosthesis function which are missed at echocardiography or fluoroscopy</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: Pts with prosthetic valves in whom obstruction was suspected but no cause found</td>
<td>N/A</td>
<td>N/A</td>
<td>CT identified morphologic etiology of obstruction in 8 of 13 pts, confirmed at surgery in 6 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Findings by CT: Sub-prosthetic substrate – 8 pts Leaflet motion restriction - 7 pts</td>
<td></td>
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</tr>
<tr>
<td>Treatment</td>
<td>Name</td>
<td>Date</td>
<td>Episodes</td>
<td>Obstructive/Nonobstructive</td>
<td>Complete success (%)</td>
</tr>
<tr>
<td>--------------</td>
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<td>------</td>
<td>----------</td>
<td>---------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Gupta</td>
<td>2000</td>
<td>110</td>
<td>110</td>
<td>81</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Lengyl</td>
<td>2001</td>
<td>85</td>
<td>54/31</td>
<td>86</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Tong</td>
<td>2004</td>
<td>107</td>
<td>99/14</td>
<td>76</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Caceres-origa</td>
<td>2006</td>
<td>68</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Roudaut</td>
<td>2009</td>
<td>127</td>
<td>115/12</td>
<td>71</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Karthikeyan</td>
<td>2009</td>
<td>120</td>
<td>120</td>
<td>63</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Nagy</td>
<td>2009</td>
<td>62</td>
<td>52/10</td>
<td>77</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Keuleers</td>
<td>2011</td>
<td>13</td>
<td>13</td>
<td>61</td>
</tr>
<tr>
<td>TT prior 2013</td>
<td>Ozkun</td>
<td>2013</td>
<td>220</td>
<td>105/106</td>
<td>83</td>
</tr>
<tr>
<td>TT overall before 2013</td>
<td></td>
<td></td>
<td>75 +/- 8</td>
<td>14 +/- 8</td>
<td>22 +/- 6</td>
</tr>
<tr>
<td>Surgery</td>
<td>Deveri</td>
<td>1991</td>
<td>106</td>
<td>106</td>
<td>100</td>
</tr>
<tr>
<td>Study Type</td>
<td>Year Published</td>
<td>Study Type/Design; Study Size</td>
<td>Patient Population</td>
<td>Endpoints and Results</td>
<td>Comment(s) / Summary/ Conclusion</td>
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<td>----------------------------------</td>
</tr>
</tbody>
</table>
| Jander et al. 2012  
(130)  
2000772 | Study type: Retrospective Size: n= 6 pts | Inclusion criteria: Pts presenting with obstructive BPV (of all pts who received a single stented bioprosthetic AV); 01/2007-12/2008; single hospital. | Endpoints: MPG  
Results:  
- 5 pts were started on phenprocoumon and followed for 114±54 d.  
- Follow-up MPG 23.5±6 mm Hg (from peak of 57.0±10 mm Hg). | All 6 pts had received a porcine valve, were hemodynamically stable, and were taking ASA 100 mg/d.  
- Echocardiography showed an increase in MPG early postoperatively from 23.3±4–57.0±10 mm Hg (p <0.001).  
- No adverse events were observed with phenprocoumon.  
- The authors concluded that 'oral anticoagulation with phenprocoumon is a safe and effective treatment in clinically stable pts with obstructive BPVT, thus obviating repeat valve surgery or thrombolysis'. |  |
<p>| Butnaru, et al | Study type: Inclusion criteria: 9 pts with clinical or |  | Endpoints: echocardiographic findings (transvalvular gradient, thrombus) | 5 of the 9 pts presented with HF symptoms at 16±12 mo after implantation. |  |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Retrospective</td>
<td>n=9 pts</td>
<td>echocardiographic evidence of valve malfunction were identified after screening 149 consecutive pts who underwent MVR with a bioprosthesis; 2002-2011; single center</td>
<td></td>
<td>Mitral BVPT thrombosis occurred in 9 pts (6%). Of those, 6 pts received anticoagulation with resolution of the echocardiographic findings (reduction in gradients; complete thrombus resolution).</td>
</tr>
<tr>
<td>2015</td>
<td>Retrospective</td>
<td>n=31 pts</td>
<td>pts diagnosed with BPVT; 1997-2013; single institution</td>
<td>MPG, clinical outcomes (NYHA class, death, stroke, embolic events)</td>
<td>Pts treated initially with VKA group (N = 15) were compared to surgery/thrombolysis (N = 17); [non-randomized]. VKA and surgery/thrombolysis decreased MPG to a similar extent: VKA group: 13±5–6 ±2 mm Hg in mitral position, 9 ± 3–5 ± 1 mm Hg in tricuspid position and 39±3–24±7 mm Hg in aortic/pulmonary position; non-VKA group: 16 ± 12–5 ± 1 mm Hg in mitral, 10 ± 5–4 ± 1 mm Hg in tricuspid and 57 ± 9–18 ± 6 mm Hg in aortic position (p=0.59 for group effect). NYHA class improved in 11 of 15 pts in the VKA group and 10 of 17 pts in the non-VKA group (p=0.39). No deaths, strokes or recognized embolic events in either group.</td>
</tr>
<tr>
<td>2015</td>
<td>Retrospective</td>
<td>n=187 pts</td>
<td>Study analyzed data from 55 pts in a TAVR clinical trial, and 2 single-center registries of 132 pts undergoing either TAVR or surgical AV bioprosthesis implantation</td>
<td>4D CT imaging (for reduced leaflet motion detection), clinical outcomes</td>
<td>Therapeutic anticoagulation with warfarin (as compared with DAPT), was associated with lower incidence of reduced leaflet motion (0% and 55%, respectively, p=0.01 in the clinical trial; and 0% and 29%, respectively, p=0.04 in the pooled registries). In pts reevaluated with follow-up CT: restoration of leaflet motion was noted in all 11 pts who were receiving anticoagulation and only 1 of 10 pts not receiving anticoagulation (p=0.001).</td>
</tr>
<tr>
<td>2015</td>
<td>Retrospective</td>
<td>n=26 pts</td>
<td>Pts with THV thrombosis (from a cohort of 4266 pts undergoing TAVR), 01/2008-09/2013, 12 centers.</td>
<td>frequency/time frame, clinical/echocardiographic and treatment correlates of THV thrombosis</td>
<td>THV thrombosis definition: (1) THV dysfunction 2° to thrombosis diagnosed based on response to anticoagulation therapy, imaging or histopathology; or (2) mobile mass detected on THV suspicious of thrombus, irrespective of dysfunction and in absence of infection. 26 (0.61%) pts had THV thrombosis after TAVR implantation; median time to thrombosis post-TAVR: 181 d (interquartile range, 45-313); most common clinical presentation: exertional dyspnea (65%).</td>
</tr>
</tbody>
</table>
Anticoagulation resulted in a significant decrease in AV MPG in 88% of pts within 2 mo.

The authors concluded: ‘THV thrombosis is a rare phenomenon that was detected within the first 2 y after TAVR and usually presented with dyspnea and increased gradients. Anticoagulation seems to have been effective and should be considered even in pts without visible thrombus on echocardiography.’

De Marchena, et al. 2015 
(134) 2594644

Study type: Retrospective
Size: n=4 pts

Inclusion criteria: Pts with THV thrombosis

Endpoints: Pathological/clinical correlates of early thrombosis after TAVR

Results:
- 2 of the 4 cases had increasing MPG post-TAVR.
- 1 case was medically treated with oral anticoagulation with normalization of gradients.
- All 3 pathology cases showed presence of a valve thrombosis in at least 2 bioprosthetic leaflets on autopsy (not previously visualized by echocardiogram)

The authors did a complimentary literature review and found 18 cases of early valve thrombosis after TAVR: in 12 of those, early anticoagulation therapy resolved the thrombus formation and normalized pressure gradients.

The authors concluded: “Consideration should be given to treatment with dual antiplatelet therapy and oral anticoagulation in pts post-TAVR with increasing mean pressure gradients and maximum aortic valve velocity”.

Data Supplement 9. Clinical Outcomes With VIV Procedures (Sections 11.7.3 and 11.8.3)

<table>
<thead>
<tr>
<th>Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Endpoints and Results</th>
<th>Comment(s) / Summary/ Conclusion</th>
</tr>
</thead>
</table>
| Ye J, et al, 2015 (135) 26476608 | Study type: registry
Size: n=73 pts (of whom 42 had VIV for bioprosthetic AV). | Inclusion criteria: pts with aortic (n=42) and mitral (n=31) bioprosthetic valve dysfunction undergoing transcatheter VIV implantation (2007-2013).
Exclusion criteria: N/A | Endpoints: 30-d outcomes; mid/long-term survival, NYHA
Results: Overall success rate: 98.6%.
At 30 d: All-cause mortality: 1.4%, Disabling stroke 1.4%, Life-threatening bleeding: 4.1%, AKI requiring hemodialysis 2.7%, Coronary artery obstruction requiring intervention 1.4%.
At 2-y follow-up, 82.8% of aortic VIV pts were in NYHA functional class III. Estimated survival rates were 88.9%, 79.5%, 69.8%, 61.9%, and 40.5% at 1, 2, 3, 4, and 5 y, respectively. | • This has the longest follow-up (Median follow-up: 2.52 y with a maximum of 8 y) of all registries transcatheter aortic and mitral VIV implantation.
• Only Edwards balloon-expandable transcatheter valves (Edwards Lifesciences Inc., Irvine, California) were used.
• The small surgical valve size (19 and 21 mm) was an independent risk factor for reduced survival in aortic VIV pts.
• Transcatheter VIV procedures can be performed safely with a high success rate and minimal early mortality and morbidity, and provides encouraging mid/long-term clinical outcomes. |

| Dvir D, et al. 2012 (90) 23052028 | Study type: multinational registry (data collected retrospectively and prospectively) | Inclusion criteria: Either CoreValve or Edwards SAPIEN devices are included
Exclusion criteria: N/A | Endpoints: Procedural success; adverse procedural outcomes; post-VIV gradients; 30 d mortality and NYHA III, 1-y survival. | • The was the first large, comprehensive evaluation of a transcatheter approach for failed surgically inserted aortic bioprostheses
• Pts receiving VIV in the stenosis group had worse 1-y survival (76.6%) in comparison with the regurgitation group (91.2%) and the combined group |
### Study Descriptions

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinational registry (data retrospectively for cases performed before registry initiation and prospectively)</td>
<td>n=459 pts</td>
<td>Pts with degenerated bioprosthetic valves undergoing VIV implantation (2007-2013)</td>
<td>VIV procedures performed using other devices than the self-expandable CoreValve (Medtronic) and balloon expandable Edwards SAPIEN devices (Edwards Lifesciences), or implanted in positions other than the aortic position.</td>
<td>1-y Kaplan-Meier survival rate: 83.2% (95% CI: 80.8–84.7%). Within 1 mo: death: 7.6%; major stroke 1.7%; Survivors with NYHA I/II: 92.6%.</td>
</tr>
<tr>
<td>Case series</td>
<td>n=24 pts (of whom 10 pts had VIV in the aortic position)</td>
<td>24 high-risk pts with failed bioprosthetic valves (n=10 were in the aortic position).</td>
<td>N/A</td>
<td>Procedural success and complications, 30-d mortality. In the 10 pts with VIV in the aortic position: VIV implantation was uniformly successful with excellent improvement in valve function, no major morbidity. 30 d mortality: 0%.</td>
</tr>
<tr>
<td>Prospective web-based multicenter registry.</td>
<td>n=24</td>
<td>Pts treated with the VIV technique for severe PVL following TAVR.</td>
<td>N/A</td>
<td>Major adverse cerebrovascular and cardiac events and prosthesis performance at 30 d and midterm follow-up. The VIV technique was used in 3.6% of all 663 TAVR pts.</td>
</tr>
</tbody>
</table>

### Results

- **Procedural success:** 93.1% of cases.
- **Adverse procedural outcomes:**
  - Initial device malposition in 15.3% of cases.
  - Ostial coronary obstruction in 3.5% of cases.
- **95% of pts had ≤1 degree of AR.**
- **Post-VIV maximum/ mean gradients:** 28.4 ± 14.1/ 15.9 ± 8.6 mm Hg, and
- **At 30 d:** All-cause mortality: 8.4% of pts; NYHA functional class I/II: 84.1% of pts.
- **1-y survival:** 85.8% survival of treated pts.
- **(83.9%) (p=0.01).**
- Having a small surgical bioprosthesis and baseline prosthesis stenosis (vs. regurgitation) were the 2 factors independently associated with 1-y mortality.
- The VIV procedure is clinically effective in the vast majority of pts with degenerated bioprosthetic valves.
- Safety and efficacy concerns include device malposition, ostial coronary obstruction, and high gradients after the procedure.

- **Implanted devices included both balloon- and self-expandable valves.**
- Pts with at least a moderate degree of both stenosis and regurgitation were included in the combined group.
- Pts in the stenosis group had worse 1-y survival (76.6%) in comparison with the regurgitation group (91.2%) and the combined group (83.9%) (p=0.01).
- Factors associated with 1-y mortality: small surgical bioprosthesis (≤21 mm) & baseline stenosis (vs. regurgitation).

- **Transcatheter VIV implantation is a reproducible option for the management of selected pts with bioprosthetic valve failure.**
- The aortic, pulmonary, mitral, and tricuspid tissue valves may be amenable to this approach.

- **The VIV group was a subpopulation from 663 consecutive pts who underwent TAVR with the 18-F CoreValve ReValving System (Medtronic, Inc., Minneapolis, Minnesota) at 14 centers across Italy.**
- The study demonstrated that transcatheter aortic VIV after TAVR using the 3rd-generation CoreValve ReValving System is feasible, safe, and
In the transcatheter aortic VIV group:
30 d major adverse cerebrovascular and cardiac events: 0%.
30-d mortality: 0%.
12 mo major adverse cerebrovascular and cardiac events: 14.1%.
12 mo mortality: 13.7%.

Thus, following TAVR, the VIV technique offers a viable therapeutic option in pts with acute significant PVL without recourse to emergent surgery.

<table>
<thead>
<tr>
<th>Study type: Retrospective observational study</th>
<th>Study type: multicenter registry</th>
<th>Study type: 3-center registry (prospectively collected data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong> Pts with degenerated surgically implanted BHVs undergoing aortic VIV procedures</td>
<td><strong>Inclusion criteria:</strong> High-risk pts with a failed aortic bioprosthesis</td>
<td><strong>Inclusion criteria:</strong> Pts undergoing aortic balloon-expandable TAVR due to THV failure with acute severe AR.</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
</tr>
<tr>
<td><strong>Endpoints:</strong> Procedural success, complications, 30-d mortality.</td>
<td><strong>Endpoints:</strong> Procedural success, 30-d complications, short-term survival, NYHA.</td>
<td><strong>Endpoints:</strong> Procedural success; 30-d/1-y mortality, mean gradient, PVL.</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td><strong>Results:</strong></td>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td>• The transcatheter aortic VIV was technically successful in all pts (2 pts requiring bailout implantation of a second TAVR prostheses for severe regurgitation during the procedure).</td>
<td>• Success rate was 100%; no procedural death.</td>
<td>• Procedural success: 90%.</td>
</tr>
<tr>
<td>• Vascular access complications: 13%.</td>
<td>• At 30 d: Deaths 12%; MI: 8%; Pacemaker implantation: 12%; At a mean follow-up of 6 mo, survival rate of 84%; NYHA functional class improved in all pts to III.</td>
<td>• Mortality at 30 ds and 1 y: 14.3% and 24%, respectively.</td>
</tr>
<tr>
<td>• Renal failure requiring dialysis: 9%.</td>
<td>• AR was paravalvular in 18 pts and transvalvular in the remaining 3 pts.</td>
<td>• After successful procedure: • Mean gradient reduced from 37 ± 12 mm Hg–13 ± 5 mm Hg (p&lt;0.01); AVA increased from 0.64 ± 0.14–1.55 ± 0.27 cm² (p&lt;0.01); PVL was none in 4 pts, mild in 13 pts, and moderate in 2 pts.</td>
</tr>
<tr>
<td>• 30-d mortality: 17% (3 of 8 fatalities the result of non-valve-related septic complications).</td>
<td>• At one-y, the mean transaortic gradient was 15 ± 4 mm Hg, which was higher than in pts undergoing conventional TAVR (11 ± 4 mm Hg, p=0.02).</td>
<td>• At 1-y follow-up: 1 pt had moderate and the others had mild/no PVL.</td>
</tr>
</tbody>
</table>

Multicenter (n=11) from Germany and Switzerland.
Both transfemoral (n = 25) or transapical (n = 22) approaches.
The transcatheter aortic VIV can be performed with high technical success rates, acceptable post-procedural valvular function, and excellent functional improvement.
In this elderly high-risk pts with multiple comorbidities, transcatheter aortic VIV was associated with 17% mortality, often because of septic complications arising in the post-operative phase.
Bapat, 2012 (141) 23140962

**Study type:** single-center case-series  
**Size:** n=23  
**Inclusion criteria:** pts undergoing a VIV procedure with the Edwards Sapien valve to treat a failing AV bioprosthesis (2008-2010).  
**Exclusion criteria:** N/A  
**Endpoints:** procedural success, short-term mortality, gradient.  
**Results:**  
- Procedural success: 100% (1 pt needed a second valve).  
- Mean gradient was reduced from 31.2 ± 17.06 mm Hg–9.13 ± 4.9 mm Hg.  
- In-hospital and/or 30-d mortality: 0%.  
- 13 pts had predominantly bioprosthetic stenosis, and the remaining had mostly regurgitation.  
- Most VIV procedures (21/23) were performed via the transapical route.  
- The transcatheter VIV is a safe and feasible alternative to treat high-risk pts with failing aortic bioprostheses.

Linke, et al 2012 (142) 23048050

**Study type:** single-center observational study  
**Size:** n=27  
**Inclusion criteria:** Consecutive symptomatic pts with failing AV bioprosthesis & aged ≥65 y & logistic EuroSCORE ≥10%; an inner diameter of the previously implanted bioprosthesis: 18.5-27 mm; ascending aorta diameter ≤45 mm above the sinotubular junction; access vessels ≥6 mm.  
**Exclusion criteria:** N/A  
**Endpoints:** procedural and short-term outcomes, 30-d mortality  
**Results:**  
- No intraprocedural death or MI.  
- Using VARC criteria:  
  - major stroke: 7.4%.  
  - life-threatening bleeding: 7.4%.  
  - kidney failure stage III: 7.4%. Major access site complication 11.1%.  
  - 30-d mortality: 7.4%.  
- Failure of bioprosthetic valves may be safely corrected by TF implantation of MCV, irrespective of the failure mode and the bioprosthesis valve type.  
- VIV implantation can be performed completely percutaneously under conscious sedation.  
- VIV implantation results in marked, instantaneous improvement in hemodynamics, which remains evident at long-term follow-up.

Ihlberg, L et al. 2013 (143) 23998786

**Study type:** multicenter registry, retrospective.  
**Size:** 45  
**Inclusion criteria:** All transcatheter VIV procedures the Nordic countries between 2008 and 2012.  
**Exclusion criteria:** N/A  
**Endpoints:** Periprocedural and postoperative outcomes (assessed using the VARC criteria).  
**Results:**  
- No intra procedural mortality.  
- Technical success: 95.6%.  
- All-cause 30-d mortality: 4.4%.  
- 30-d major complications: stroke: 22%, Periprocedural MI: 4.4%, major vascular complication: 2.2%.  
- At 1 mo, all but 1 pt had either no or mild PVL.  
- 1 y survival: 88.1%.  
- The type of failure was stenosis/ combined in 58% & regurgitation in 42% of cases.  
- The SAPIEN/XNT (Edwards LifeSciences, Irvine, CA) and CoreValve (Medtronic Inc, Minneapolis, Minn) systems were used.  
- Access (transapical, transfemoral, transaortic, and subclavian).  
- Mean follow-up: 14.4 mo.  
- Transcatheter VIV is widely performed in most centers in the Nordic countries. The short-term results were excellent in this high-risk pt population, demonstrating a low incidence of device- or procedure-related complications.

Camboni, et al 2015 (144) 25881576

**Study type:** prospective single-center registry  
**Size:** 31  
**Inclusion criteria:** Pts undergoing VIV procedure at single institution since 2009.  
**Exclusion criteria:** TAVR pts not undergoing VIV (608 pts)  
**Endpoints:** Procedural success, 30-d survival, post-VIV regurgitation.  
**Results:**  
- Procedural success: 88%.  
- Post-procedural regurgitation: trace in 23% and moderate in 13% of pts.  
- 30-d survival: 77% with a significantly improved NYHA class of 1.79 ± 0.58 (p=0.001).  
- Pts were provided with 5 Medtronic CoreValves, 15 Edwards SapienXT, 1 Edwards Sapien 3, 7 Medtronic Engager, and 3 Symetis Acurate TA valves. The left main stem was occluded in 1 pt (Sapien XT 26 in a Mitroflow 25 mm) who underwent emergent  
- Jeopardizing coronary blood flow was likely in stenotic and calcified bioprostheses, particularly in tubelike aortic sinuses.  
- The investigators concluded that ‘Planning, imaging, and the use of valves
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Endpoints</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conradi, et al 2015 (145) 26403870</td>
<td>registry (prospectively-collected data)</td>
<td>Consecutive pts receiving VIV procedures from 2008 to 2014 at a single center</td>
<td>procedural success and complications, short-term mortality, trans-AV gradients.</td>
<td>Overall VIV success rate: 97.3%.</td>
<td>This registry reported a single-center cumulative experience using 6 types of THVs in all anatomic positions. VIV can be performed in all anatomic positions with acceptable hemodynamic and clinical outcome in high-risk pts allowing commissural alignment as well as leaflet capturing seem to reduce the risk.</td>
</tr>
<tr>
<td>Duncan BF, et al 2015 (146) 26215358</td>
<td>case series, single center</td>
<td>consecutive pts with failing stentless bioprostheses</td>
<td>short-mid-term mortality, procedural complications.</td>
<td>30-d predicted mortality STS score: 14%, all had severe AR and highly symptomatic, all underwent TAVI with a self-expanding device. The aortic VIV procedure may be performed in high-risk pts with a degenerate stentless bioprosthesis with low 30-d and 1-y mortality rates.</td>
<td></td>
</tr>
<tr>
<td>Erlebach, et al 2015 (147) 26543594</td>
<td>retrospective single-center observational study</td>
<td>All consecutive pts undergoing VIV vs. redo surgical AVR (2001-2014).</td>
<td>post-procedural complications, 30-d mortality, 1-y survival</td>
<td>Postoperative pacemaker implantation and chest tube output were higher in the reoperation surgical group compared to the TAV-in-SAV group [11 (21%) vs. 3 (6%), p=0.042 and 0.9±1.0 vs. 0.6±0.9, p=0.047, respectively]. NS differences in MI, stroke, dialysis postoperatively, or 30-d mortality. 1-y survival was significantly lower in the VIV group (83% vs. 96%, p&lt;0.001).</td>
<td>Pts in the VIV group were significantly older, had a higher logistic EuroSCORE and a lower LVEF. Both groups, irrespective of different baseline comorbidities, show very good early clinical outcomes. While redo surgery is still the standard of care, a subgroup of pts may profit from the transcatheter VIV procedure.</td>
</tr>
<tr>
<td>Ye, et al. 2015 (148) 26476608</td>
<td>registry</td>
<td>pts with aortic (n= 42) and mitral (n= 31) bioprosthetic valve dysfunction undergoing transcatheter VIV implantation (2007-2013).</td>
<td>30-d outcomes; mid/long-term survival, NYHA</td>
<td>Overall success rate: 98.6%.</td>
<td>This has the longest follow-up (Median follow-up: 2.52 y with a maximum of 8 y) of all registries transcatheter aortic and mitral VIV implantation. Only Edwards balloon-expandable transcatheter valves (Edwards Lifesciences Inc., Irvine, California) were used. The small surgical valve size (19 and 21 mm) was an independent risk factor.</td>
</tr>
<tr>
<td>Study type: systematic review</td>
<td>Exclusion criteria: N/A</td>
<td>Inclusion criteria: Pts undergoing transcatheter aortic VIV implantation and redo conventional AVR</td>
<td>Exclusion criteria: N/A</td>
<td></td>
<td></td>
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</tbody>
</table>

At 30 d:
- All-cause mortality: 1.4%, Disabling stroke 1.4%,
- Life-threatening bleeding: 4.1%,
- AKI requiring hemodialysis 2.7%,
- Coronary artery obstruction requiring intervention 1.4%.

At 2-y follow-up, 82.8% of aortic VIV pts were in NYHA functional class I/II.
Estimated survival rates were 88.9%, 79.5%, 69.8%, 61.9%, and 40.5% at 1, 2, 3, 4, and 5 y, respectively.

Phan, et al 2016 (149) 26904259

Study type: systematic review
Size: n=823 pts (18 studies)

Inclusion criteria: Pts undergoing transcatheter aortic VIV implantation and redo conventional AVR

Exclusion criteria: N/A

1° endpoints:
- Perioperative/30 d mortality
Other endpoints:
- PVLs
- Stroke
- Bleeding
- MI
- AKI
- Vascular complications
- Pacemaker implantation
- Mean Gradient
- Peak Gradient

Results:
- Perioperative mortality (VIV:7.9% vs. cAVR:6.1%, p=0.35)
- PVLs (VIV:3.3% vs. cAVR: 0.4%, p=0.022)
- Stroke (VIV:1.9% vs. cAVR:8.8%, p=0.002
- Bleeding (VIV:5.9% vs. cAVR:9.1%, p=0.014)
- Mean Gradient (VIV: 38 mm Hg preoperatively to cAVR: 15.2 mm Hg postoperatively, p=0.001)
- Peak Gradient (VIV: 59.2 to cAVR: 23.2 mm Hg, p=0.0003).

- Similar hemodynamic outcomes achieved with VIV as compared to redo conventional AVR
- Lower risk of strokes and bleeding in VIV compared to redo conventional AVR
- Higher PVL rates in VIV compared to redo conventional AVR

*Selective contemporary studies of transcatheter VIV procedures for failed bioprosthetic valves (excluding small studies with <20 pts).*
### Data Supplement 23. *(Updated From 2014 Guideline)* Selective Studies on Surgical and Catheter-based Closure for Paravalvular Regurgitation (Section 11.8.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Endpoints</th>
<th>Adverse Events/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orszulak 1983 (150) 686002</td>
<td>To report outcome with surgical reoperation for PVR</td>
<td>Retrospective N=105</td>
<td>Surgical reoperative repair of prosthetic PVR</td>
<td>Aortic PVR (n=75) and mitral PVR (n=29)</td>
<td>Early mortality for entire cohort: 5.7%. 5-y survival was 94% for aortic PVR pts and 75% for mitral PVR pts.</td>
<td>N/A</td>
</tr>
<tr>
<td>Miller 1995 (151) 8566176</td>
<td>To identify clinical features that predict occurrence of PVR. Outcome after surgical repair also reported</td>
<td>Retrospective N=30</td>
<td>Surgical reoperative repair of aortic prosthetic PVR</td>
<td>Aortic prosthetic PVR</td>
<td>30-d survival=90%; 5-d survival=72%</td>
<td>N/A</td>
</tr>
<tr>
<td>Akins 2005 (152)</td>
<td>To examine acute and long-term outcome of surgery for PVR</td>
<td>Retrospective N=136</td>
<td>Surgical reoperative repair of aortic or mitral prosthetic PVR</td>
<td>Mitral PVR in 68% Aortic PVR in 32%</td>
<td>Operative mortality, 6.6% Perioperative stroke, 5.1% 10-y survival, 30%</td>
<td>N/A</td>
</tr>
<tr>
<td>Pate 2006 (153) 16969856</td>
<td>To describe outcome in series of pts undergoing percutaneous repair of PVR</td>
<td>Retrospective N=10 (10 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=9) and aortic PVR (n=1); 9 were not surgical candidates</td>
<td>7 with successful procedure 3 pts died at 1 y</td>
<td>6 with reduction in regurgitation 5 with NYHA improvement by 1 class</td>
</tr>
<tr>
<td>Shapira 2007 (154) 17578053</td>
<td>To examine the feasibility and early outcome of percutaneous repair of PVR</td>
<td>Retrospective N=11 (13 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=8), aortic PVR (n=1), and both aortic and mitral PVR (n=2) Estimated surgical mortality, 17.8%</td>
<td>10 with device deployment 6 with reduction in regurgitation 5 with NYHA improvement by 1 class</td>
<td>Hemolysis improved in 4, worsened in 4, and was unchanged in 2 in early follow-up 3 deaths in follow-up</td>
</tr>
<tr>
<td>Cortes 2008 (155) 18237605</td>
<td>To examine utility of TEE in percutaneous repair of PVR</td>
<td>Retrospective N=27 (27 defects)</td>
<td>TEE before and procedure (n=27) and at follow-up ≥1 mo (n=17)</td>
<td>Mechanical mitral PVR in pts at high risk for surgery</td>
<td>62% with procedure success TEE helped guide procedure and identified variety of complications</td>
<td>N/A</td>
</tr>
<tr>
<td>Ruiz 2011 (156) 22078427</td>
<td>To examine feasibility and efficacy of the percutaneous repair of PVR</td>
<td>Retrospective/ N=43 (57 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>Mitral PVR (n=36), aortic PVR (n=9), and both aortic and mitral PVR (n=2)</td>
<td>Device deployment success in 86% of pts and 86% of leaks Survival: 92% at 6 m, 86% at 18 m</td>
<td>12 pts required multiple procedures; reduction in need for transfusions or erythropoietin from 56%–5%; NYHA class improved by ≥1 in 2 device embolizations 1 emergency surgery 1 vascular complication 1 procedural death</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Title</td>
<td>Study Design</td>
<td>N</td>
<td>Procedure</td>
<td>Device</td>
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<tr>
<td>Soraja 2011</td>
<td>2011</td>
<td>To examine the feasibility and early outcome of percutaneous repair of PVR</td>
<td>Retrospective</td>
<td>N=115 pts (141 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>78% mitral PVR, 22% aortic PVR</td>
</tr>
<tr>
<td>Soraja 2011</td>
<td>2011</td>
<td>To determine the long-term clinical efficacy of percutaneous repair of PVR</td>
<td>Retrospective</td>
<td>N=126 (154 defects)</td>
<td>Percutaneous repair of PVR</td>
<td>79% mitral PVR, 21% aortic PVR</td>
</tr>
<tr>
<td>Nijenhuis 2014</td>
<td>2014</td>
<td>To determine the safety and clinical efficacy of transcatheter PVL closure using an open transapical approach</td>
<td>Prospective</td>
<td>N= 36</td>
<td>Transcatheter PVL closure using an open transapical approach</td>
<td>Consecutive pts (mean age 67±12 y, STS score 7±4%). All had severe symptomatic PVL in the mitral (81%) or aortic (19%) position</td>
</tr>
<tr>
<td>Taramasso 2014</td>
<td>2014</td>
<td>To compare the in-hospital outcomes of pts who underwent surgery and TA closure for PVL</td>
<td>Retrospective</td>
<td>N = 139</td>
<td>Surgery vs. TA-closure for PVL</td>
<td>122 pts (87.3%) underwent surgical treatment (66% mitral PVL; 32% aortic PVL) and 17 pts (12.2%) underwent a transcatheter closure via a surgical TA approach. (all the pts had mitral PVL; 1 case had combined mitral and aortic PVLs).</td>
</tr>
<tr>
<td>Gafoor 2014</td>
<td>2014</td>
<td>To determine the safety and efficacy of percutaneous PVL closure after TAVR</td>
<td>Retrospective</td>
<td>n= 5</td>
<td>Percutaneous closure of PVL</td>
<td>Pts who received TAVR with self-expandable valves</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Purpose</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruz-Gonzales, I (162) 25037539</td>
<td>Retrospective</td>
<td>To analyze the feasibility and efficacy of PVL closure with the Amplatzer Vascular Plug III</td>
<td>n= 33 percutaneous closure of PVL 33 pts with 34 PVLs (27 mitral, 7 aortic)</td>
<td>Successful device implantation: 93.9% (in 2 pts, a 2nd planned procedure was needed). Successful closure (defined as regurgitation reduction ≥1 grade): 90.9% At 90 d: Survival: 100%. Significant clinical improvement: 90.3%. • Emergency surgery due to disc interference (n=1) • Blood transfusion (n=3) • No procedure-related death, MI, or stroke • 4 pts developed vascular complications (pseudoaneurysm) at 90 d</td>
</tr>
<tr>
<td>Millan 2015 (163) 25746018</td>
<td>Systematic review/ Meta-analysis</td>
<td>To assess whether a successful transcatheter PVL reduction is associated with improvement in clinical outcomes</td>
<td>n= 362 pts successful vs. failed transcatheter PVL reductions 12 clinical studies that compared successful and failed transcatheter PVL reductions</td>
<td>Compared with a failed intervention, a successful transcatheter PVL reduction was associated with lower cardiac mortality (OR: 0.08; 95% CI: 0.01–0.90) A successful transcatheter PVL reduction was associated with: • Superior improvement in functional class or hemolytic anemia. (OR: 9.95; 95% CI: 2.10–66.73). • Fewer repeat surgeries (OR: 0.08; 95% CI: 0.01–0.40).</td>
</tr>
<tr>
<td>Goktekin 2016 (164) 26897292</td>
<td>Case series</td>
<td>To evaluate early and midterm outcomes of percutaneous PVL closure utilizing a novel device (Occlutech PVL Device)</td>
<td>n=21 consecutive symptomatic and inoperable pts who had moderate or severe paravalvular prosthetic regurgitation on TEE</td>
<td>≥1 grade reduction in regurgitation was achieved in all pts. No deaths due to any cause, stroke or surgery for prosthetic impingement, worsening or relapse of PVL occurred at follow-up (90 d and 12 mo) No in-hospital mortality. 1 case of hemothorax in 1 pt and 1 case of pneumothorax in another</td>
</tr>
</tbody>
</table>
### Data Supplement 24. (Updated From 2014 Guideline) Surgical Outcome in IE (Section 12.2.3)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Primary Endpoint</th>
<th>Predictors of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jault, 1997 (165)</td>
<td>Identify significant predictors of operative mortality, reoperation, and recurrent IEs</td>
<td>Retrospective single-center surgical cohort study</td>
<td>247</td>
<td>NVE alone; surgery 100%</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>Operative mortality was 7.6% (n=19). Overall survival rate (operative mortality excluded) was 71.3% at 9 y. The probability of freedom from reoperation (operative mortality included) was 73.3±4.2% at 8 y. The rate of IE of the implanted prosthetic valve was 7%.</td>
<td>Increased age, cardiogenic shock at the time of operation, insidious illness, and greater thoracic ratio (&gt;0.5) were the predominant risk factors for operative mortality; the length of antibiotic therapy appeared to have no influence. Increased age, preoperative neurologic complications, cardiogenic shock at the time of operation, shorter duration of the illness, insidious illness before the operation, and MV endocarditis were the predominant risk factors for late mortality.</td>
</tr>
<tr>
<td>Castillo 2000 (166)</td>
<td>To determine the clinical features and long-term prognosis of IE in pts who were not drug users.</td>
<td>Prospective single-center case series</td>
<td>138</td>
<td>NVE 69%, PVE 31%; surgery 51%</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>Severe complications (HF, embolic phenomenon, severe valve dysfunction, abscesses, renal failure, and immunologic phenomenon) occurred in 83% of pts. 51% of pts underwent surgery during the active phase (22% was emergency surgery) Inpt mortality was 21%. Overall 10 y survival was 71%</td>
<td>There were no significant differences in survival depending on the type of treatment received during the hospital stay (medical vs. combined medical-surgical) in this observational study.</td>
</tr>
<tr>
<td>Alexiou 2000 (167)</td>
<td>Single-center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late</td>
<td>Retrospective single-center surgical cohort study</td>
<td>118</td>
<td>NVE 70%, PVE 30%; 100% of pts underwent surgery</td>
<td>Registration of epidemiological and microbiological features, echocardiography data, treatment strategy</td>
<td>Operative mortality was 7.6% (9 pts). Endocarditis recurred in 8 (6.7%). A reoperation was required in 12 (10.2%). There were 24 late deaths, 17 of them cardiac. Actuarial freedom from recurrent endocarditis, reoperation, late cardiac death, and long-term survival at 10 y were 85.9%, 87.2%, 85.2%, and 73.1%, respectively.</td>
<td>Predictors of operative mortality: HF, impaired LV function. Predictors of recurrence: PVE. Predictors of late mortality: myocardial invasion, reoperation. Predictors of poor long-term survival: coagulase-negative staphylococcus, annular abscess, long ICU stay.</td>
</tr>
<tr>
<td>Wallace, 2002 (193)</td>
<td>To identify clinical markers available within the first 48 h of admission that are associated with poor outcome in IE</td>
<td>Retrospective single-center cohort study</td>
<td>208</td>
<td>NVE 68%, PVE 32%; surgery 52%</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy</td>
<td>Mortality at discharge was 18% and at 6 mo 27%. Surgery was performed in 107 (51%) pts. In-hospital mortality was not influenced by surgery (23% vs. 15% in the nonsurgical group); p=0.3 At 6 mo there was a trend towards increased mortality in the surgical group (33% vs. 20%)</td>
<td>Duration of illness, age, gender, site of infection, organism, and LV function did not predict outcome. Abnormal white cell count, raised creatinine, ≥2 major Duke criteria, or visible vegetation conferred poor prognosis.</td>
</tr>
</tbody>
</table>

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Hasbun, 2003  
To derive and externally validate a prognostic classification system for pts with complicated left-sided native valve IE  
Retrospective multicenter cohort study  
513  
Pts with left-sided NVE with current indication of surgery in 45%  
Registration of clinical information, sociodemographic data, comorbidity conditions, previous heart disease, symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings  
In the derivation and validation cohorts, the 6-mo mortality rates were 25% and 26%, respectively. In the derivation cohort, pts were classified into 4 groups with increasing risk for 6-mo mortality: 5%, 15%, 31%, and 59% (p<0.001). In the validation cohort, a similar risk among the 4 groups was observed: 7%, 19%, 32%, and 69% (p<0.001).  
5 baseline features were independently associated with 6 mo mortality (comorbidity [p=0.03], abnormal mental status [p=0.02], moderate-to-severe congestive HF [p=0.01], bacterial etiology other than viridans streptococci [p<0.001 except S. aureus, p=0.004], and medical therapy without valve surgery [p=0.002]).

Vikram, 2003  
To determine whether valve surgery is associated with reduced mortality in pts with complicated, left-sided native valve IE  
Retrospective multicenter cohort study; Propensity analysis  
513  
Pts with left-sided NVE with current surgical intervention in 45%  
Registration of clinical information, sociodemographic data, comorbidity conditions, previous heart disease, symptoms, physical findings, blood cultures, ECG, echocardiography, type of surgery performed, and operative findings  
After adjustment for baseline variables associated with mortality (including hospital site, comorbidity, HF, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection), valve surgery remained associated with reduced mortality (adjusted HR: 0.35; 95% CI: 0.23–0.54; p<0.02). In further analyses of 218 pts matched by propensity scores, valve surgery remained associated with reduced mortality (15% vs. 28%; HR: 0.45; 95% CI: 0.23–0.86; p=0.01). After additional adjustment for variables that contribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR: 0.40; 95% CI: 0.18–0.91; p=0.03). In this propensity-matched group, pts with moderate-to-severe congestive HF showed the greatest reduction in mortality with valve surgery (14% vs. 51%; HR: 0.22; 95% CI: 0.09–0.53; p=0.001).  
Pts with moderate-to-severe HF showed the greatest reduction in mortality with valve surgery. Stratifying the data by congestive HF among propensity-matched pts undergoing surgery revealed that among pts with none to mild HF, valve surgery was not associated with reduced mortality compared with medical therapy (HR: 1.04; 95% CI: 0.43–2.48; p=0.93). Among propensity-matched pts with moderate-to-severe HF, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR: 0.22; 95% CI: 0.08–0.53; p=0.01).

Halib, 2005  
To identify prognostic markers in 104 pts with PVE and the effects of a medical vs. surgical strategy outcome in PVE  
Retrospective multicenter cohort study  
104  
100% PVE pts; surgery 49%  
Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy  
Overall, 22 (21%) died in hospital. By multivariate analysis, severe HF (OR: 5.5) and S. aureus infection (OR: 6.1) were the only independent predictors of in-hospital death. Among 92 in-hospital survivors, 21 (26%) died during a 32 mo follow-up. Mortality was not significantly different between surgical and nonsurgical pts (17% vs. 25%, respectively, not significant). Both in-hospital and long-term mortality were reduced by a surgical approach in high-risk subgroups of pts with staphylococcal PVE and complicated PVE.  
Factors associated with in-hospital death were severe comorbidity (6% of survivors vs. 41% of those who died; p=0.05), renal failure (28% vs.45%, p=0.05), moderate- to-severe regurgitation (22% vs. 54%; p=0.06), staphylococcal infection (16% vs. 54%; p=0.001), severe HF (22% vs. 64%; p=0.001), and occurrence of any complication (60% vs. 90%; p=0.05).
Revilla, 2007  
(171)  
17052690  
Describe the profile of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality  
Prospective multicenter cohort study  
608  
NVE 66%, PVE 34%; surgery studied for the present report  
Brucella, Q fever, Legionella, and Mycoplasma. Persistent infection despite appropriate antibiotic treatment (31%).  
Of these 508 episodes, 132 (34%) were electively operated on, and 89 pts required urgent surgery (defined as prior to completion of antibiotic course). 1° reasons for urgent surgery in these 89 pts were HF that did not respond to medication (72%) and persistent infection despite appropriate antibiotic treatment (31%). 32 pts (36%) died during their hospital stay. 32% of NVE died vs. 45% of pts with PVE. Late PVE was associated with a higher mortality than early PVE (53% vs. 36%)  
Univariate analysis identified renal failure, septic shock, Gram-negative bacteria, persistent infection, and surgery for persistent infection as factors associated with mortality. Multivariate analysis confirmed only persistent infection and renal insufficiency as factors independently associated with a poor prognosis.

Hill, 2007  
(172)  
17158121  
Analyze epidemiology, optimal treatment, and predictors of 6-mo mortality in IE  
Prospective single-center cohort study  
193  
NVE 66%, PVE 34%; surgery 63%  
Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy  
43% included staphylococci, 26% streptococci, and 17% enterococci. At least 1 complication occurred in 79% of the episodes and 63% had surgical intervention. 6-mo mortality was 22%; 33% for staphylococci, 24% for enterococci, and 8% for streptococci. 74% of pts with a contraindication to surgery died when compared with 7% with medical treatment without a contraindication and 16% with surgical treatment.  
S. aureus, contraindication to surgery (present in 50% of deaths).

Remadi, 2007  
(173)  
17383330  
To evaluate the predictors of outcome and to establish whether early surgery is associated with reduced mortality  
Prospective multicenter cohort study  
116  
S. aureus IE alone; NVE 83%, PVE 17%; surgery 47%  
Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Antibiotic treatment.  
In-hospital mortality rate was 26%, and the 36-mo survival rate was 57%. Surgical group mortality was 16% vs. 34% in the medically treated group (p<0.05)  
In unadjusted analyses, early surgery performed in 47% of pts was associated with lower in-hospital mortality (16% vs. 34%; p=0.034) and with better 36-mo survival (77% vs. 39%; p<0.001).  
Multivariate analyses identified comorbidity index, HF, severe sepsis, prosthetic valve IE, and major neurologic events as predictors of in-hospital mortality  
Severe sepsis and comorbidity index were predictors of overall mortality  
After adjustment of baseline variables related to mortality, early surgery

Akso, 2007  
(174)  
17205442  
To better understand the impact of surgery on the long-term survival of pts with IE  
Prospective single-center cohort study with propensity score matching  
426  
NVE 69%, PVE 19%, "other" 12%; surgery in 29%  
Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Pts' propensity scores for surgery  
The fit of the propensity model to the data was assessed using the concordance index with pts who underwent surgery matched to those who did not undergo surgery, using individual propensity scores. The following factors were statistically associated with surgical therapy: age, transfer from an outside hospital, evidence of IE on physical examination, the presence of infection with staphylococci, HF, intracardiac abscess, and hemodialysis without a chronic catheter.  
Revealed that surgery was associated with decreased mortality (HR: 0.27; 95% CI: 0.13–0.55). A HX of DM (HR: 4.81; 95% CI: 2.41–9.62), the presence of chronic IV catheters at the beginning of the episode (HR: 2.65; 95% CI: 1.31–5.33), and with increased mortality.

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<p>| Tleyjeh, 2007 (175) 17372170 | To examined the association between valve surgery and all-cause 6 mo mortality among pts with left- sided IE | Matched propensity analysis | 546 | NVE alone; surgery 24% | Propensity score to undergo valve surgery was used to match pts in the surgical and nonsurgical groups. To adjust for survivor bias, the follow-up time was matched so that each pt in the nonsurgical group survived at least as long as the time to surgery in the respective surgically-treated pt. | Death occurred in 99 of the 417 pts (23.7%) in the nonsurgical group vs. 35 deaths among the 129 pts (27.1%) in the surgical group. 18 of 35 (51%) pts in the surgical group died within 7 d of valve surgery. | After adjustment for early (operative) mortality, surgery was not associated with a survival benefit (adjusted HR: 0.92; 95% CI: 0.48–1.76). |
| Tleyjeh, 2008 (176) 18308866 | To examine the association between the timing of valve surgery after IE dx and 6-mo mortality among pts with left-sided IE | Retrospective single-center cohort propensity analysis | 546 | NVE alone; surgery 24% | The association between time from IE dx to surgery and all-cause 6 mo mortality was assessed using Cox proportional hazards modeling after adjusting for the propensity score (to undergo surgery 0–11 d vs. &gt;11 d, median time, after IE dx). | The median time between IE dx and surgery was 11 d (range 1–30). Using Cox proportional hazards modeling, propensity score and longer time to surgery (in d) were associated with unadjusted HRs of (1.15, 95% CI: 1.04–1.28, per 0.10 unit change; p=0.009) and (0.93; 95% CI: 0.88–0.99, per d; p=0.03), respectively. | On univariate analysis, a longer time to surgery showed a significant protective effect for the outcome of mortality. After adjusting for the propensity to undergo surgery early vs. late, a longer time to surgery was no longer significant, but remained in the protective direction. |
| Thuny, 2009 (177) 19329497 | To determine whether the timing of surgery could influence mortality and morbidity in pts with complicated IE | Retrospective single-center cohort propensity analysis | 291 | NVE 82%, PVE 18%; surgery 100% | The time between the beginning of the appropriate antimicrobial therapy and surgery was used as a continuous variable and as a categorical variable with a cut-off of 7 d to assess the impact of timing of surgery. 2 groups of pts were formed according to the timing of surgery: the &quot;&lt;1st wk surgery group&quot; and the &quot;&gt;1st wk surgery group&quot;. The impact of the timing of surgery on 6 mo mortality, relapses, and PVD was analyzed using PS. 1st wk surgery was associated with a trend of decrease in 6-mo mortality in the quintile of pts with the most likelihood of undergoing this early surgical management (quintile 5: 11% vs. 33%, OR: 0.18, 95% CI: 0.04 –0.83; p=0.03). Pts of this subgroup were younger, were more likely to have S. aureus infections, congestive HF, and larger vegetations. &lt;1st wk surgery was associated with an increased number of relapses or PVD (16% vs. 4%, adjusted OR: 2.9, 95% CI: 0.99–8.40; p=0.05). | Very early surgery (&lt;7 d) associated with improved survival (especially in highest risk pts), but greater likelihood of relapse or post-operative valve dysfunction. |</p>
<table>
<thead>
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<th>Study</th>
<th>Design</th>
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<td>Manne, 2012 (178) 22206953</td>
<td>Retrospective single-center surgical cohort study</td>
<td>NVE 58%, PVE 42%; surgery 100%</td>
<td>Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy</td>
<td>Overall 90% of pts survived to hospital discharge. When compared with pts with NVE, pts with PVE had significantly higher 30-d mortality (13% vs. 5.6%; p&lt;0.01), but long-term survival was not significantly different (35% vs. 29%; p=0.19). Pts with IE caused by S. aureus had significantly higher hospital mortality (15% vs. 8.4%; p&lt;0.05), 6 mo mortality (23% vs. 15%; p=0.05), and 1 y mortality (28% vs. 18%; p=0.02) compared with non-S. aureus IE.</td>
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<td>Kang, 2012 (179) 22738096</td>
<td>Prospective randomized trial at 2 centers with intention to treat analysis</td>
<td>Left-side NVE and high risk of embolism to early surgery (49%) vs. conventional treatment (51%)</td>
<td>Pts were randomly assigned in a 1:1 ratio to the early-surgery group or the conventional-treatment group with the use of a Web-based interactive response system. The protocol specified that pts who were assigned to the early-surgery group should undergo surgery within 48 h after randomization. Pts assigned to the conventional-treatment group were treated according to AHA guidelines, and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted</td>
<td>The 1° endpoint (composite of in-hospital death and embolic events that occurred within 6 wk after randomization) occurred in 1 pt (3%) in the early surgery group as compared with 9 (23%) in the conventional-treatment group (HR: 0.10; 95% CI: 0.01–0.82; p=0.03). There was no significant difference in all-cause mortality at 6 mo in the early-surgery and conventional- treatment groups (3% and 5%, respectively; HR:0.51; 95% CI: 0.05–5.66; p=0.59). The rate of the composite en point of death from any cause, embolic events, or recurrence of IE at 6 mos was 3% in the early-surgery group and 28% in the conventional-treatment group (HR: 0.08; 95% CI: 0.01–0.66; p=0.02). As compared with conventional treatment, early surgery in pts with IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.</td>
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To establish guidelines for the surgical treatment of pts with IE who have cerebrovascular complications.

Retrospective study of 181 pts with cerebral complication among 2523 surgical cases of IE.

Questionnaire consisting of 2 parts: (1) Each center was asked for a summary of the number and outcome of pts with IE according to the types of IE (active/healed and native valve/prosthetic valve) and the presence of cerebral complications; (2) the other portion inquired about each pt with cerebral complications, asking for details such as age, gender, AF, anticoagulant therapy, diseased valve, organism, effectiveness of antimicrobial therapy, reason for early cardiac operation, interval between the onset of symptoms and the cardiac operation, type of cerebral complication, cerebral aneurysm, prior cerebral surgery, severity, influence of operation on cerebral damage, and outcome.

To study the influence of cardiac surgery on preoperative cerebral complications, we analyzed the interval between the onset of cerebral complications and performance of the cardiac operation, as well as other preoperative variables. The effectiveness of antimicrobial therapy was ranked in 3 grades (1 = ineffective, 2 = effective, and 3 = well controlled). A correlation between the interval and the exacerbation of cerebral complications was evaluated by means of the Spearman rank correlation coefficient. The intervals were then classified in several groups, and variability between the groups for the exacerbation was estimated by Scheffe's F procedure for post-hoc comparisons, according to the Kruskal-Wallis test. To analyze the risk factors affecting exacerbation of cerebral complications, we expressed preoperative variables as mean ± standard error. The difference between the groups with and without exacerbation was tested for significance by the unpaired t test, and incidence was expressed as percentage of pts having the variable compared with the entire group of pts and then compared by χ2 analysis. Moreover, all variables and incidence (transformed to continuous variables) were estimated by stepwise regression analysis. Statistical significance was accepted at a p level of <0.05. These analyses were done with the Stat View system (Abacus Concepts, Inc., Berkeley, Calif.).

The rate of exacerbation of cerebral complications decreased to 10% in pts who underwent surgical treatment more than 15 d after cerebral infarction and to 2.3% in those operated on more than 4 wk later. Preoperative risk factors were severity of cerebral complications, interval from onset of symptoms to operation, and uncontrolled HF as the indication for cardiac surgery. More than 15 d after cerebral hemorrhage, the risk of the progression of cerebral damage is still significant, and this risk persists even 4 wk later.

Assess the incidence of neurological complications in pts with infective endocarditis, the risk factors for their development, their influence on the clinical outcome, and the impact of cardiac surgery.

Retrospective analysis of prospectively collected data on a multicenter cohort.

Specific variables from registries were analyzed including the date of IE dx; pts age and sex; type of endocarditis (native or prosthetic); location and size of vegetations on echocardiography; infecting microorganism; date, type, and extent of neurological complications; anticoagulant therapy given; date of the start of antimicrobial treatment; date of surgery (if performed); and outcome.

Specific variables were analyzed including the date of IE dx; pts age and sex; type of endocarditis (native or prosthetic); location and size of vegetations on echocardiography; infecting microorganism; date, type, and extent of neurological complications; anticoagulant therapy given; date of the start of antimicrobial treatment; date of surgery (if performed); and outcome.

Predicators of neurological complications were vegetation size ≥3 cm (HR: 1.91; 95% CI: 1.07–3.43; p=0.029), S aureus as the cause of IE (HR: 2.47; 95% CI: 1.94–3.15; p<0.001), anticoagulant therapy at IE dx (HR: 1.31; 95% CI: 1.00–1.72; p=0.048), and MV involvement (HR: 1.29; 95% CI: 1.02–1.61; p=0.03). Further analysis showed that elderly pts (≥70 y) had lower complication rates than younger ones, and only hemorrhagic events showed statistical significance (HR: 0.36; 95% CI: 0.16–0.83; p=0.014). Anticoagulant treatment was particularly associated with cerebral hemorrhage (HR: 2.71; 95% CI: 1.54–4.76; p=0.001).
| Barsic, B., 2013 (182) | Examine the relationship between the timing of surgery after stroke and the incidence of in-hospital and 1-y mortalities. | Post-hoc review of the International Collaboration on Endocarditis–Prospective Cohort Study of with definite IE who were admitted to 64 centers June 2000–December 2006 | 198 pts | 198 pts of 857 pts with IE complicated by ischemic stroke who underwent valve replacement surgery post-stroke | Data were obtained from the International Collaboration on Endocarditis–Prospective Cohort Study of 4794 pts with definite IE who were admitted to 64 centers from June 2000 through December 2006. Multivariate logistic regression and Cox regression analyses were performed to estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates. | Estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates. | After adjustment for other risk factors, early surgery was not significantly associated with increased in-hospital mortality rates (OR: 2.308; 95% CI: .942–5.652). Overall, probability of death after 1-y follow-up did not differ between 2 treatment groups (27.1% in early surgery and 19.2% in late surgery group, p=.328; adjusted HR: 1.138; 95% CI: .802–1.650). |


