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POSTGRADUATE COURSE IN

ADVANCED CARDIOLOGY

Diagnosis and Management of Valvular Heart Disease

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Outline/Table of Content

LEARNING OBJECTIVES

By the end of this chapter, learners will be able to:

- Describe the epidemiology and pathophysiology of valvular heart disease
- Recognize physical exam findings associated with each of the valvular diseases
- Discuss the diagnostic testing and hemodynamic findings in each of the valvular disease
- Discuss the medical treatment and identify indications for surgical or percutaneous treatment options

Introduction

Valvular heart disease is a major cause of cardiovascular morbidity and mortality around the world. Rheumatic heart disease (RHD) is still the leading cause of heart valve disease in India and other developing countries, whereas age-related degenerative valve disease is the most common cause in the U.S (1). This chapter will discuss the etiology, pathophysiology, clinical manifestations, invasive and noninvasive evaluation and the treatment strategies of valvular disease that is manifested in adulthood.

Aortic Stenosis

Overview

In the US, about two-thirds of all heart valve surgeries are for aortic valve replacement, most of which are done for severe aortic stenosis (AS). In India, isolated AS, more common in males, is the third most common valve lesion constituting about 7% of cases (2). There is still a larger group of patients with mild to moderate AS who requires continued medical management and accurate diagnosis. Until recently, surgical valve replacement for severe degenerative AS was the preferred intervention. However, with the recent advances in technology, transcutaneous aortic valve implantation has gained its place in the armamentarium.

Epidemiology and Etiology

Bicuspid aortic valve (BAV) is the most common congenitally abnormal valve, constituting about 1–2 % of the general population with a 2:1 male to female ratio (3). It can occur as an isolated lesion or associated with aortopathy presenting with dilated aortic root or ascending aorta, coarctation of aorta, supravalvular AS, supramitral ring, or hypoplastic arch/left ventricle. Early calcific degeneration can cause severe AS in the fifth and sixth decades of life, requiring surgical replacement. There is evidence that a familial form of bicuspid valve is present in about 20–30% of cases and screening for first-degree relatives is recommended when bicuspid aortic valve is identified in an individual (4). Unicuspid aortic valves often lead to severe obstruction in infancy but rare cases are seen in adulthood. Supravalvular stenosis and discrete subvalvular membrane are other forms of congenital AS and the treatment is limited to surgical repair when the hemodynamic effects are significant.

Calcific aortic valve disease of a normal trileaflet valve was once thought to be due to age-related degeneration from mechanical stress over years, but is now recognized to be due to an active process similar to atherosclerosis, involving lipid accumulation, inflammation, and calcification (5). Aortic sclerosis, defined as the aortic valve calcification and thickening in the absence of outflow obstruction, is a progressive disease and approximately 10–15% of patients develop some degree of aortic

stenosis over a period of 2 to 5 years (6,7). Severe AS usually develops in seventh or eighth decade of life. In patients with abnormal calcium homeostasis, such as in end-stage renal disease, AS can progress earlier in life. In a systemic search of multiple databases, the prevalence of any degree of AS in patients >75 years of age was 12.4% and severe AS was present in 3.4% (8).

Rheumatic AS is uncommon in the Western world and is often accompanied with rheumatic mitral stenosis. In an echocardiographic study, incidence of isolated rheumatic AS in tertiary care centers in South India was 1.1%, whereas combination of rheumatic MS and AS was 2.4% (2).

Pathophysiology and Natural Progression

AS is a progressive disease where outflow obstruction gradually worsens over a prolonged period. Left ventricular outflow obstruction results in chronic LV pressure overload, increased LV diastolic pressure and an increased LV ejection time. The increase in LV systolic pressure leads to left ventricular hypertrophy to maintain adequate cardiac output, but increased cell mass and interstitial fibrosis results in LV diastolic dysfunction. Increased LV ejection time leads to a decrease in myocardial perfusion time (diastolic time) and increased oxygen demand, all of which results in myocardial ischemia and subsequent LV systolic dysfunction. Pulmonary hypertension can occur due to chronically elevated left atrial pressure. Loss of atrial contraction (i.e. atrial fibrillation) or tachycardia during exercise can result in symptoms (9).

The severity of AS is defined by the valve anatomy, hemodynamics and symptoms. According to the most recent ACC Valvular Heart Disease guidelines published in 2014, classification of progression of valvular heart disease was described by 4 stages (4). (Table 1) outlines the stage of AS.

Table 1: Progression of Aortic Stenosis

Stage	Definition	Valve Anatomy	Hemodynamics	Consequences
A	At risk of AS	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax < 2 m/s	None
B	Progressive AS	Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion Rheumatic valve changes with commissural fusion	Mild AS: Aortic Vmax < 2 m/s or MG < 20 mmHg Moderate AS: Aortic Vmax 3.0-3.9 m/s or MG 20–39 mmHg	Early diastolic dysfunction may be present Normal LVEF
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥ 4 m/s or MG ≥ 40 mmHg AVA typically is ≤ 1.0 cm^2 (or AVAi ≤ 0.6 $cm2/m^2$	LV diastolic dysfunction Mild LVH Normal LVEF

Table 1: Progression of Aortic Stenosis (table contd...)

Stage	Definition	Valve Anatomy	Hemodynamics	Consequences
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/s or MG ≥40 mmHg AVA typically ≤1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2)	LVEF < 50
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/s or MG ≥40 mmHg AVA typically ≤1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2) but may be larger with mixed AS/AR	LVEF < 50
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1.0 cm^2 with resting aortic Vmax < 4 m/s or MG < 40 mmHg DSE shows AVA ≤1.0 cm^2 with Vmax < 4 m/s at any flow rate	LVEF < 50
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1.0 cm^2 with Vmax < 4 m/s or MG < 40 mmHg AVAi ≤0.6 cm^2/m^2 and Svi < 35 mL/m^2 Measured when patient is normotensive (systolic BP < 140 mmHG)	Increased LV relative to wall thickness Small LV size with low SV Restrictive diastolic filling LVEF ≥50%

AR indicates aortic regurgitation; **AS**, aortic stenosis; **AVA**, aortic valve area; **AVAi,** aortic valve area indexed to body surface area; **BP**, blood pressure; **HF**, heart failure; **LV**, left ventricular; **LVH**, left ventricular hypertrophy; **LVEF**, left ventricular ejection fraction; **MG**, mean transaortic gradient; and **Vmax**, maximum aortic velocity
(*Adapted from*: Nishimura et al. *J Am Coll Cardiol*. 2014;63:e57(4).)

Clinical Manifestations

Dyspnea with exertion often precedes angina, which is the result of myocardial ischemia in the absence of significant obstructive coronary artery disease (CAD). However, half of patients with severe AS have concomitant obstructive CAD. Syncope or pre-syncope is most often due to inadequate cerebral perfusion in the setting of peripheral vasodilation in the presence of fixed left ventricular outflow obstruction. At later stages, AS can lead to sudden death. Rarely, extension of calcification of the valve into the conduction system can cause atrioventricular block.

Aortic stenosis can be complicated by an increased risk of bleeding, particularly from the gastrointestinal tract. This syndrome is thought to be due to an acquired type 2A von Willebrand deficiency. Increased shear stress from the high-velocity flow through

the aortic valve leads to a conformational change in von Willebrand multimers, resulting in increased degradation of these large multimers (6,10,11).

Evaluation

Physical Exam:

Classical physical exam finding in severe AS is the late-peaking systolic crescendo-decrescendo murmur that radiates to the carotids with a decrease in intensity of the second heart sound and a slow-rising, late-peaking, low-amplitude carotid pulse. The murmur of AS increases in intensity with maneuvers that increase the stroke volume, such as squatting, which can be used to differentiate AS from hypertrophic cardiomyopathy. On the other hand, maneuvers that increase the afterload, such as handgrip, will decrease the difference in pressure gradient between the left ventricle and aorta resulting in a decrease of the murmur of AS while increasing the intensity of mitral regurgitation. (Table 2) shows maneuvers that can be used to differentiate systolic heart murmurs. The cardiac impulse at the apex is usually sustained and some patients may have palpable fourth heart sound (S4) due to vigorous left atrial contraction into the noncompliant hypertrophied ventricle.

Table 2: Maneuvers to Differentiate Systolic Murmurs

Murmurs	Increased Preload Rapid squatting, passive leg raising)	Decreased Preload (Valsalva, standing)	Increased Afterload (Handgrip)	Decreased Afterload (Amyl nitrate)
AS	Increase	Decrease	Decrease	Increase
MR	Increase	Decrease	Increase	Decrease
MVP	Decrease with later onset click	Increase with early onset click	Decrease with later onset click	Increase with early onset click
HOCM	Decrease	Increase	Decrease	Increase

Echocardiography:

Echocardiography is now the mainstay of AS evaluation and offers a simple, reliable, and noinvasive method to follow patients. Three main echocardiographic parameters are used to grade the severity of AS: the peak transaortic velocity, the mean transaortic gradient, and the aortic valve area (AVA), which is calculated using the continuity equation. (Table 1) shows the cut-off values for each stage of AS. (Table 3) shows advantages and disadvantages of the three criteria. Integrating all criteria along with performing a comprehensive analysis of the ventricular size and function, LV stroke volume, degree of aortic and mitral regurgitation is vital to accurate assessment of severity of AS.

Table 3: Advantages and Disadvantages for Echocardiographic Criteria for Assessment of AS			
Criteria	**Formula/Method**	**Advantages**	**Disadvantages**
Peak transaortic velocity	Direct measurement	Direct	Requires parallel alignment of ultrasound beam, flow dependent
Mean gradient		Comparable to invasive measurements	Requires accurate velocity measurement, flow dependent
Aortic valve area		Relatively flow dependent	Depends on accurate LVOT diameter measurement, which is prone to errors

(*Adapted from*: Osnabrugge et al. *J Am Soc Echocardiogr*. 2017;30(4):372-92 (12.)

Discordant findings, where mean gradient <40 mmHg and/or peak velocity <4 m/sec, but AVA is < 1 cm^2, are not uncommon and should first prompt assessment of the accuracy of data collected. The most common technical pitfall that may lead to an erroneous calculated AVA is an underestimation of the LVOT diameter measurement. Multiwindow interrogation with optimal alignment of the continuous-wave Doppler beam with the direction of aortic flow jet is important to obtain the most accurate measurement of peak aortic jet velocity and mean gradient. The dimensionless index (also known as velocity ratio or velocity time integral (VTI) ratio) is an approach to reduce errors related to LVOT measurements and is calculated by dividing the LVOT velocity (or VTI) by the AS velocity (or VTI). This ratio reaches 1 in the absence of valve stenosis. Severe stenosis is present when the ratio is 0.25 (12). The role of indexing body size to the valve area is controversial because the valve area does not increase with excess body weight. However indexing valve area is important in children, adolescents, and small adults as valve area may seem severely narrowed when only moderate stenosis is present. As such, American Society of Echocardiography recommends calculation of indexed aortic valve when height is less than 135 cm, body surface area is less than 1.5 m^2, or body mass index is less than 22. In these cases, dimensionless valve index (DVI) can also be utilized (12).

If the technical measurement errors are eliminated and there is still low-gradient AS with a low AVA, diagnosis of low-flow, low-gradient AS (LF-LG AS) should be considered. 2014 ACC/AHA Valvular Heart Disease Guidelines define two types of low gradient AS:

1. Classical low-flow, low gradient (LF-LG) AS
    a. MG <40 mmHg, stroke volume index (SVi) <35 mL/msq, and LVEF < 50%
    b. Low-dose (up to 20 mcg/kg) dobutamine stress echocardiogram (DSE) should be performed to assess contractile reserve and to differentiate between pseudosevere AS (lack of aortic valve opening due to low flow) from true severe AS.
    i. If there is flow (contractile) reserve (i.e., >20% increase in stroke volume) and an increase in MG to >40 mmHg or Vmax > 4m/sec, but little or no increase in

AVA, then diagnosis of true severe AS is made. If there is an increase in AVA to above 1cm^2 with little or no increase in MG or Vmax, findings are consistent with pseudo-severe AS.

ii. If there is no flow reserve (i.e lack of increase in stroke volume > 20%), diagnosis is more challenging. Aortic valve calcium score by multidetector cardiac computer tomography (MDCT) has been shown to be an independent marker of AS severity and mortality and can be utilized to diagnose severe AS. Aortic valve calcium score ≥1200 Agatston units (AU) for women and ≥2000 AU for men have been proposed to differentiate severe AS (13,14). Alternatively, for patients who have some degree of flow reserve that does not reach 20% cut-off, projected valve area at a normal flow rate can be calculated from the formula: AVAproj=AVArest+VC • (250 Qrest).

2. Paradoxical LF-LG AS

   a. MG <40 mmHg, SVi <35 ml/m², and LVEF >50%

   b. Assessment of factors contributing to low stroke volume is essential. It is commonly seen in women with small and hypertrophied ventricles, atrial fibrillation, significant mitral regurgitation, severe uncontrolled hypertension. There is often restrictive physiology leading to reduced stroke volume.

   c. Cardiac catheterization with aortic valve gradient measurement and nitroprusside challenge should be considered.

   i. Reduction of afterload and LV filling pressures with nitroprusside can allow discrimination of patients with moderate rather than severe A (15).

On the other hand, in some patients with high-transvalvular flow (eg. concomitant aortic regurgitation, shunt lesions, fever, anemia, and hyperthyroidism) valve area may be 1 cm^2 despite a mean gradient ≥40 mmHg. In these situations, the left ventricle is still experiencing the hemodynamic effects of severe aortic stenosis and after the reversible causes are excluded, treatment of AS should be undertaken based on the guidelines.

Biomarkers in Aortic Stenosis:

In patients with asymptomatic AS, biomarkers such as natriuretic peptides including brain natriuretic peptide (BNP) and N-terminal proBNP have been shown to be potential indicators of disease severity, and BNP levels appear to be a strong independent predictor of cardiovascular death (16,17). Some studies suggest patients with highest BNP levels may require closer follow up and eventual early valve replacement; however, larger clinical trials are required for use in clinical practice (18).

Stress Testing in AS:

In patients with severe AS who are asymptomatic, exercise treadmill testing (ETT) is safe and recommended to evaluate the exercise tolerance and hemodynamic response. Decreased exercise tolerance, symptoms of AS, or lack of increase or a decrease in systolic blood pressure with exercise are indications for AVR. It is important to rule out the following contraindications to ETT before performing the test:

1. An established indication for AVR
2. Uncontrolled hypertension
3. Symptomatic or hemodynamically significant arrythmias
4. Inability to perform the test such as orthopedic limitations. Significant ventricular arrhythmias and/or ischemia can be observed due to concomitant coronary artery disease

Multidetector Cardiac Computed Tomography (MDCT):

With the advent of transcutaneous aortic valve replacement (TAVR), MDCT has gained popularity as it can measure annulus area, leaflet length, the annular to coronary ostial distance, and aortic root anatomy, which are parameters used for valve type and sizing. MDCT also provides information on minimal luminal diameters of peripheral arteries and vessel tortuosity for assessment of optimal vascular access for TAVR, atherosclerotic plaque burden, presence of aneurysms or thrombi and is essential in determining feasibility of TAVR. More recently, quantification of aortic valve calcification score has been shown to correlate with severity of AS and can be useful in diagnosing severe AS in low-flow states (13,14).

Cardiac Catheterization:

When noninvasive testing is inconclusive or discordant with physical exam findings and symptoms, invasive assessment of the AS gradient is indicated. Mean aortic gradient (MG) is measured directly, cardiac output (CO) is derived from Fick's or thermodilution technique, and the Gorlin formula or the Hakki equation are used to calculate aortic valve area (AVA) as follows:

- **Gorlin Formula:** $AVA = CO / (44.3 * HR * SEP * \sqrt{MG})$
- **Hakki Equation:** $AVA = CO / \sqrt{MG}$

(**HR**= heart rate; **SEP**= systolic ejection period)

Pre-TAVR Assessment:

Once severe AS is diagnosed with TTE and TAVR is considered based on surgical risk or frailty, patients should be referred to a heart valve center for optimal management. Standard pre-TAVR workup includes surgical and frailty risk scoring, routine blood tests, pulmonary function tests, MDCT, carotid ultrasound, coronary angiogram, and dental evaluation with a goal to treat any acute infections prior to TAVR to avoid

prosthetic valve endocarditis. The most widely used risk scoring models for the prediction of perioperative mortality after cardiac surgeries are EuroSCORE (European System for Cardiac Operative Risk Evaluation) and the STS (Society of Thoracic Surgeons) score. AHA/ACC Valvular Heart Disease Guidelines recommends risk assessment scheme based on the STS risk score, frailty, comorbidity, and procedure-specific impediments (4). STS risk scoring has four categories, which are listed in (Table 4). The model incorporates patient characteristics such as age, gender, race, type of surgery, presence of coronary or peripheral artery disease, renal function, lung disease, medical status of the patient to predict perioperative outcomes. As discussed in more detail below, TAVR can be considered for patients with symptomatic severe AS who are at prohibitive, high, or intermediate surgical risk and for those patients who have severe comorbidities that were not adequately reflected by risk score (19–22).

Table 4: Risk Assessment for TAVR

STS Risk	% Predicted Mortality	Other Considerations
Low risk	$<4\%$	No frailty, no comorbidity, and no procedure-specific impediments
Intermediate risk	4% to 8%	No more than mild frailty or 1 major organ system compromise not to be improved postoperatively, and minimal procedure-specific impediments
High risk	$>8\%$	Moderate-severe frailty, no more than 2 major organ system compromise not to be improve postoperatively, or a possible procedure-specific impediment
Prohibitive risk	Preoperative risk of mortality or major morbidity $>50\%$ at 1 year	≥ 3 or major organ system compromise not to be improved postoperatively, severe frailty, or severe procedure-specific impediments

(*Adapted from*: Otto, et al. *J Am Coll Cardiol*. 2017;69(10): 1313-46)

Treatment

Currently, there is no medical therapy to treat or slow the progression of AS. Despite retrospective studies suggesting statins may slow the progression of AS, large-scale randomized controlled trials failed to show benefit (23,24). Natural history studies have shown that once symptoms (shortness of breath, angina, presyncope/syncope) develop, average survival is only 2–3 years. Aortic valve replacement (AVR) is effective in improving both symptoms and survival. The 2014 ACC/AHA Valvular Heart Disease guidelines recommend AVR once symptoms develop or if there is evidence of LV dysfunction caused by AS. Exercise stress testing may be useful in patients with severe AS who do not endorse symptoms. An abnormal hemodynamic response to exercise is associated with a worse prognosis in aortic stenosis and is an indication for AVR. For patients who are undergoing coronary artery bypass or other cardiac surgery, AVR is indicated if AS is moderate or severe.

Transcatheter aortic valve replacement (TAVR) has been demonstrated to be superior to medical therapy in inoperable patients and noninferior to surgical AVR in both intermediate and high surgical-risk patients. Therefore, TAVR is now a therapeutic option for patients with symptomatic severe AS who are at prohibitive, high, or intermediate surgical risk (see Table 4) (19–22). Recently, the PARTNER 3 Study showed a significantly lower rate of a combination of death, stroke, and rehospitalization at 1 year compared with surgery in a low-risk group (85) but final word from FDA and guidelines are yet to be determined. It is particularly well suited for patients of advanced age, extracardiac morbidities, including renal, liver, and lung disease, and anatomical factors that would complicate an open surgical approach (i.e. heavily calcified porcelain aorta, previous chest radiation, or a bypassed left anterior descending artery at risk for injury during sternotomy). Evaluation by a multidisciplinary heart valve team, consisting of interventional cardiologists, cardiac imagers, and cardiac surgeons, is recommended for patients who are considered for TAVR.

In the United States, there are currently two types of TAVR valves approved. The Edwards Sapien is a balloon-expandable valve designed with a cobalt-chromium frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate skirt, whereas Medtronic CoreValve Evolut consists of a tricuspid valve obtained from porcine pericardial tissue, mounted and sutured inside a self-expandable nitinol frame (Figure 1). Sapien 3 (Edwards Lifesciences) transcatheter valve is the fourth generation and is available in four sizes (20,23,26, and 29 mm). As compared to the previous generation of Sapien XT (Edwards Lifesciences), the design of the Sapien 3 frame has been modified to enhance the geometry for an ultra-low delivery profile and has an outer skirt to minimize paravalvular regurgitation. The CoreValve Evolut R device is currently available in four sizes (23,26,29, and 34 mm). The lower part of the device has a high radial force that allows for the self-expansion and exclusion of native calcified valve leaflets. As compared to the previous generation of CoreValve devices, Evolut R provides improved anatomical fit, annular sealing, and durability, and its design enables recapturability and repositionability. Evolut Pro design has a porcine pericardial tissue wrap around the outer sealing zone of the frame which provides advanced sealing and a lower incidence of paravalvular leak. Several other companies have valves in varying stages of development.

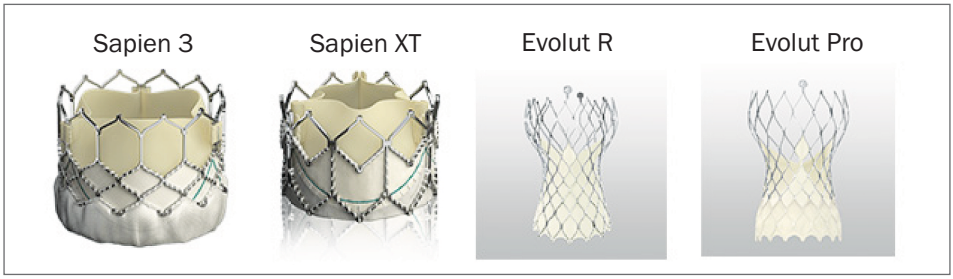


Figure 1: FDA approved TAVR valves

Patients with low-gradient AS have higher perioperative mortality ranging between 8–33% after SAVR. Nonetheless, valve replacement with SAVR or TAVR is still recommended given dismal survival rates of 40–60% at two years with conservative management (25).
(Reproduced with permission from Edwards Lifesciences and Medtronic.)

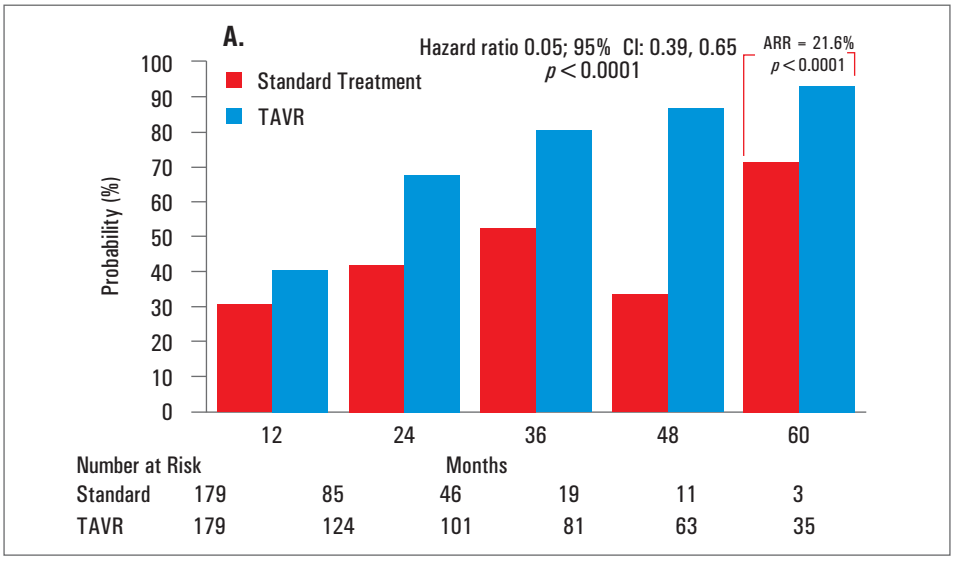
Long-term follow-up by the valve specialist for the first 30 days after the procedure, followed by subsequent formal transfer of care back to the referring cardiologist is recommended. Antithrombotic therapy should include clopidogrel 75 mg/day for the first 6 months and lifelong aspirin 75–100 mg/day. Monitoring for post-TAVR complications with echocardiography (before discharge, at 30 days, and then annually) and electrocardiography is imperative. As with all prosthetic valves, long-term dental hygiene and antibiotic prophylaxis should be implemented.

Percutaneous balloon aortic valvulopasty (BAV) is often performed in children and adolescents. In adults, although it can be useful as a bridge to definitive therapy (i.e AVR), it is associated with poor outcomes as a stand-alone therapy. The main limitations include recurrence of AS (50% within 6 months) and causing (or worsening) existing aortic regurgitation (9).

Outcomes

In the absence of AVR, outcomes of patients with symptomatic severe AS are dismal. Untreated severe AS can lead to LV dysfunction, heart failure, pulmonary hypertension, embolic events, conduction disease, and, eventually, death. Surgical AVR improves this dismal prognosis and restores survival to that expected of an age-matched and gender-matched general population without AS (26,27). While limited data exists regarding long-term outcomes of TAVR, short- and medium-term outcomes of TAVR are similar to SAVR with more vascular complications, paravalvular leak, and requirement of re-intervention (Figures 2 and Table 5). In the PARTNER 1 trial where first-generation valves were used, moderate or severe aortic regurgitation occurred in 14% in the TAVR group and 1% in the SAVR group ($p<0.001$) and was associated with increased 5-year risk of mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation versus 56.6% for those with mild aortic regurgitation or less; $p=0.003$) (28). Currently available third and fourth-generation devices with smaller delivery systems and designs to prevent paravalvular regurgitation promise better results. Main procedural

and long-term complications that are unique to TAVR along with treatment options are listed in (Table 6).



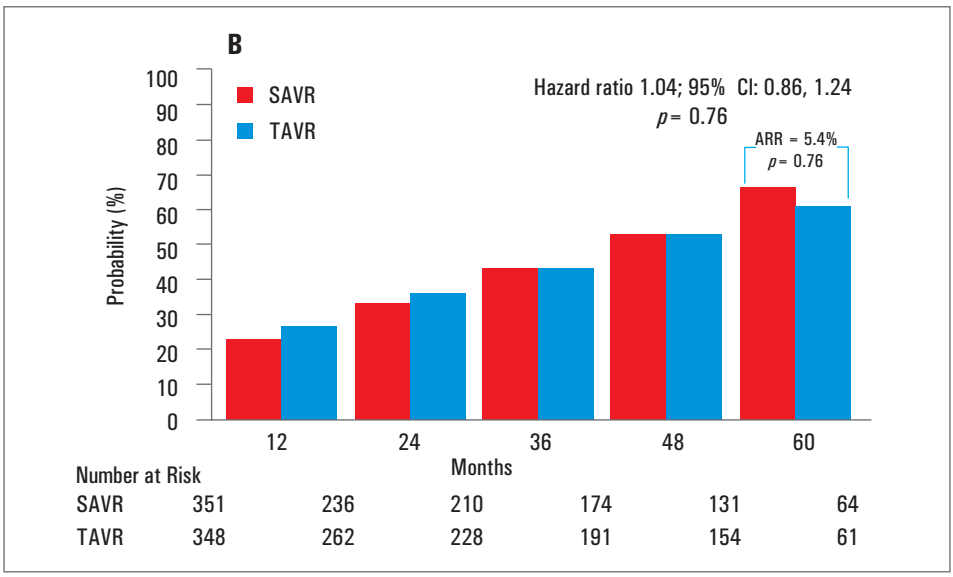


Figure 2: Outcomes of the PARTNER 1 trial using first-generation Sapien valves

(*Adapted from*: Mack et al. *Lancet.* 2015 Jun 20;385(9986):2477-84. doi:10.1016/S0140 -6736 (15) 60308-7 and Kapadia et al. *Lancet.* 2015;385 (9986):2485-91(28,29).)

Table 5. Clinical outcomes of PARTNER 1 trial at 30 days at 1 year in the intention-to-treat population in high risk patients (21)						
Outcome	**TAVR, 30 days (%)**	**SAVR, 30 days (%)**	**p-value**	**TAVR, 1 year (%)**	**SAVR, 1 year (%)**	**p-value**
Death from any cause	3.4	6.5	0.07	24.2	26.8	0.44
Major stroke	3.8	2.1	0.20	5.1	2.4	0.07
Major vascular complications	11	3.82	< 0.001	11.3	3.5	< 0.001
Major bleeding	9.3	19.5	< 0.001	14.7	25.7	< 0.001
New onset atrial fibrillation	8.6	16	0.006	12.1	17.1	0.07

Table 6. Unique TAVR procedural and long-term complications, risk factors, and management strategies		
Complications	**Risk Factor**	**Management**
Annular rupture	Small annulus size Bulky calcification of annulus or LVOT Heavily calcified bicuspid valve	Emergent surgery
Valve embolization	Valve malpositioning	Emergent surgery if in the left ventricle Recapture or deploy in the descending aorta Valve-in-valve Endovascular removal (snare)
Paravalvular regurgitation	Asymmetric leaflet or LVOT calcification	Post-dilation Paravalvular leak closure
Coronary obstruction	Low coronary height Small sinus depth Bulky heavy asymmetric valve calcification	Percutaneous coronary intervention
High-degree heart block	Pre-existing right bundle branch block and use of CoreValve	Pacemaker implantation
Subclinical valve thrombosis	Lack of antiplatlet use	Use of vitamin K antagonists or novel oral anticoagulants

Summary and Recommendations for Clinicians

1. The most common etiology of AS is calcific degeneration followed by rheumatic heart disease. Classical symptoms include shortness of breath, angina, presyncope, or syncope. Once the symptoms develop, average survival is 2 to 3 years.
2. Diagnosis and evaluation of patients with AS includes physical exam, echocardiography, cardiac catheterization, and cardiac CT.
3. AS stages are defined according to the valve anatomy, valve hemodynamics, and

hemodynamic consequences. Diagnosis of severe AS in low-gradient states can be very challenging. Dobutamine stress echocardiography is helpful in differentiating severe AS from pseudosevere AS in the setting of low-flow, low-gradient AS.

4. Aortic valve replacement is the only treatment for severe AS. AVR is indicated in patients with severe symptomatic AS, severe AS with LV dysfunction, or asymptomatic patients with severe AS and abnormal stress test. Surgically, AVR has traditionally been the treatment, but TAVR can be considered as an alternative for patients with moderate, high, or prohibitively high risk.

PULMONIC VALVE STENOSIS

Epidemiology and Etiology

Congenital pulmonic stenosis is the most common etiology and can be subvalvular, valvular, or supravalvular. Rheumatic heart disease rarely leads to pulmonic stenosis. Carcinoid disease, often presents with concomitant tricuspid valve disease, can affect the pulmonic valve and cause a mixed disease. PS is one of the features of tetralogy of Fallot (TOD). PS can also be associated with other congenital lesions such as atrial septal defect (ASD) leading to right to left shunting.

Pathophysiology and Natural Progression

Longstanding PS causes right ventricular (RV) hypertrophy due to pressure overload. In late stages, RV dysfunction and associated symptoms can be seen. If associated with ASD, right to left shunting can lead to cyanosis.

Clinical Manifestations

Patients with PS are typically asymptomatic until RV dysfunction occurs. When symptomatic, patients can present with exertional dyspnea, fatigue and right sided congestive symptoms (i.e. hepatic congestion, abdominal pain, ascites, lower extremity edema). Atrial or ventricular arrhythmias can cause syncope.

Evaluation

Physical Exam Findings:

Patients with PS may have a palpable RV heave or thrill and a harsh systolic murmur that increases with inspiration. The duration of murmur increases with severity of stenosis.

Noninvasive Imaging:

Echocardiography is the primary imaging modality for evaluation of pulmonic valve disease, right ventricular enlargement/hypertrophy and function, pulmonary arterial dilation, and associated congenital lesions. Rheumatic changes are characterized as leaflet fusion, whereas retraction and thickening of the leaflets is seen in carcinoid. Thickening with systolic doming is the hallmark of congenital PS. Subvalvular or supravalvular (main or branch pulmonary artery stenosis) stenosis can also be apparent in congenital forms of PS. Peak gradient less than 36 mmHg is considered mild PS and peak gradient >64 mmHg with mean gradient >35 mmHg is considered severe.

Treatment

In adult patients with moderate or severe PS and otherwise unexplained symptoms of heart failure, cyanosis from right-to-left shunt, and/or exercise intolerance, balloon valvuloplasty (if feasible) or surgical repair is recommended by the 2018 ACC/AHA adult congenital heart disease guidelines (81).