Chapter

Hemodynamic Classifications of Aortic Stenosis and Relevance to Prognosis

Susan Kwon and Aasha Gopal

Abstract

Hemodynamic classifications of aortic valve stenosis (AS) have important prognostic implications. In normal flow state, severe AS is defined as peak aortic velocity ≥ 4.0 m/s, mean transaortic gradient (MG) ≥ 40 mmHg, and aortic valve area (AVA) < 1.0 cm^2. However, numerous studies have shown that severe AS (based on AVA < 1.0 cm^2) with low gradient (MG < 40 mmHg) is prevalent due to low flow state, in the setting of reduced and preserved left ventricular ejection fraction (LVEF). Thus, the hemodynamic classifications of AS with AVA < 1.0 cm^2 were expanded to include the transvalvular flow state and pressure gradients. These flow-gradient patterns include normal flow/very high gradient, normal flow/high gradient, low flow/high gradient, low flow/low gradient with reduced LVEF, low flow/low gradient with preserved LVEF, and normal flow/low gradient. Among these, the low-gradient AS subgroups are challenging, particularly to differentiate true-severe AS (where aortic valve replacement is necessary) and pseudo-severe AS (where conservative management is recommended). Additional diagnostic studies such as dobutamine stress echocardiography and/or cardiac computed tomography, as well as other parameters such as projected AVA and/or valvuloarterial impedance may be helpful. This chapter will review diagnostic approaches and prognostic implications of different AS subtypes.

Keywords: aortic stenosis, classification, echocardiography, hemodynamics, low flow, prognosis

1. Introduction

Aortic valve stenosis (AS) is the most common valvular heart disease in developed countries. When symptomatic, AS is known to have significant morbidity and mortality. While the prevalence of AS is expected to rise with the aging population, there is no pharmacological treatment option to prevent its progression at this time [1, 2]. Aortic valve replacement (AVR) is the only treatment demonstrated to improve survival and symptoms [3, 4]. Therefore, in the management of patients with AS, it is essential to accurately diagnose the disease severity and determine the proper timing of surgical referral. According to the ACC/AHA guidelines, AVR is class I indication for patients with symptomatic severe AS with high transaortic mean gradient (MG) ≥ 40 mmHg and left ventricular (LV) ejection fraction (LVEF) < 50% and/or who are undergoing another surgery [5]. Over the past decade, challenges due to discrepancies with grading

High Gradient (HG) (MG ≥ 40 mmHg)	Low Gradient (LG) (MG < 40 mmHg)
NF/Very HG Normal Flow (SVI ≥ 35 ml/m²), (MG > 60 mmHg)	**LF/LG with reduced LVEF** Low Flow (SVI < 35 ml/m2), LVEF < 50%
NF/HG Normal Flow (SVI ≥ 35 ml/m²)	**LF/LG with preserved LVEF** Low Flow (SVI < 35 ml/m²), LVEF ≥ 50%
LF/HG Low Flow (SVI < 35 ml/m²)	**NF/LG** Normal Flow (SVI ≥ 35 ml/m²)
AVA, aortic valve area; MG, mean transaortic gradient; HG, high gradient; LG, low gradient; NF, normal flow; LF, low flow; SVI, stroke volume index; LVEF, left ventricular ejection fraction.	

Table 1.
Hemodynamic classification of severe aortic stenosis (AVA < 1.0 cm²).

AS severity and the necessity of integrating the valve gradient with flow patterns were recognized when a significant subset of patients were found to have small AVAs suggestive of severe AS with lower gradients despite preserved LVEF [6]. As a result, under the umbrella of severe AS (based on AVA < 1.0 cm^2), a new hemodynamic classification of AS was proposed which can be categorized into six subgroups based on LV flow state [normal flow (NF) vs. low flow (LF)] and pressure gradient [very high gradient (VHG) vs. high gradient (HG) vs. low gradient (LG)]. These six flow-gradient patterns (NF/VHG, NF/HG, LF/HG, LF/LG with reduced LVEF, LF/LG with preserved LVEF, and normal NF/LG) have shown to represent distinct pathophysiologic types of severe AS with different clinical outcomes (see **Table 1**).

2. Natural history of AS

AS is a progressive valvular heart disease with gradual valvular narrowing resulting in LV outflow tract (LVOT) obstruction over time. Degenerative calcific AS is the most common type of this disease process and predominantly affects the elderly. With this condition, there is a long latent period during which the patient is asymptomatic although there is progression of obstructive physiology at the aortic valve and LV pressure overload. Survival in asymptomatic patients undergoing conservative management with watchful waiting is not statistically different from age- and gender-matched controls [7]. However, once symptoms of angina, syncope, or heart failure develop, there is a very rapid decline. Patients with AS who develop angina have a 5-year survival, syncope 3-year survival, and heart failure, the most ominous of all, 2-year survival (see **Figure 1**) [8, 9]. Thus, when symptoms are corroborated by established echocardiographic criteria for severe AS, some form of intervention is required because these individuals only have a 3-year survival of about 25%. In severe asymptomatic AS, the rate of symptom onset is higher when significant calcification of the aortic valve is present and in older patients [7]. Other factors demonstrated to predict symptom onset and surgical outcome include brain natriuretic peptide (BNP) [10]. While the risk of sudden death is a major concern in patients with asymptomatic AS undergoing conservative management, numerous studies have shown that the risk is very low, <1% per year [7, 11, 12].

Over the years, there has been marked decrease in the operative risk of AS. Furthermore, while prior studies have shown rather benign prognosis of asymptomatic severe AS patients, suggesting that delay in surgery can be safe until the development of symptoms, there is controversy as to the optimal timing of AVR

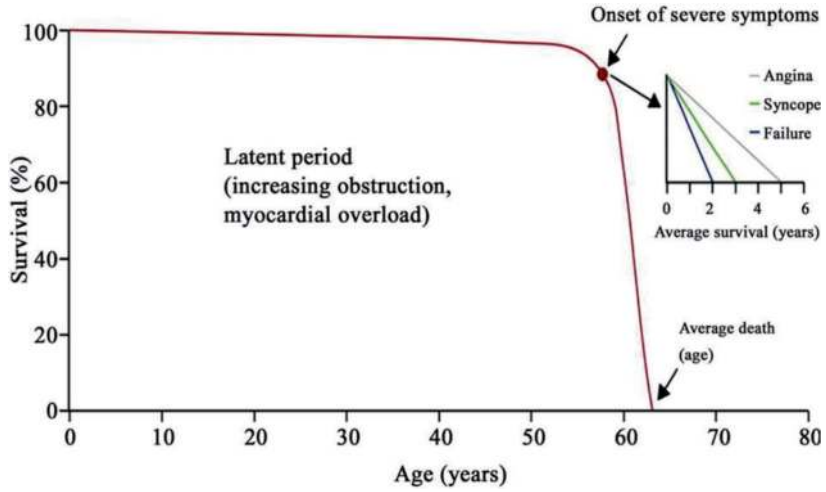

Figure 1.
Natural history of aortic stenosis. A long, latent, asymptomatic period is present followed by a very rapid decline in survival with the onset of symptoms of angina, syncope, and/or heart failure in severe AS patients [8].

and whether elective or early intervention during the asymptomatic stage might be better long term. At present, the surgical mortality for AVR is <2% for severe AS in patients with New York Heart Association (NYHA) functional class I or II heart failure, whereas this risk is significantly higher with class III or IV [13]. Thus, even though the patient may be asymptomatic, AS severity can progress and cause LV dysfunction during the conservative management period and significantly increase the surgical risk [14]. Furthermore, there is concern regarding the development of significant LV myocardial hypertrophy and irreversible myocardial fibrosis due to pressure overload which may result in persistent postoperative diastolic dysfunction and heart failure, even if AVR is successful [15, 16]. However, a general recommendation cannot be made at this time due to insufficient evidence to justify the benefit of AVR in asymptomatic patients to outweigh the risks of surgery and complications related to prosthesis long-term. However, those patients who may benefit from early surgical intervention should be identified through risk stratification [17]. Over the past decade, transcatheter aortic valve replacement (TAVR) has emerged as an alternative treatment strategy for symptomatic severe AS patients who are not suitable or prohibitive for surgical AVR (SAVR) [18, 19] or at high risk for surgery [20, 21]. This technology then expanded to benefit patients with intermediate operative risk, where TAVR using a self-expanding prosthesis was noninferior to SAVR at 24 months follow-up [22]. More recently, TAVR using a balloon-expandable SAPIEN 3 system in low-risk patients was shown to be superior to SAVR based on a composite of death, stroke, and rehospitalization at 1-year follow-up, despite excellent surgical results [23]. Long-term follow-up studies are underway to help determine the true therapeutic impact of TAVR vs. SAVR.

3. Severe AS: definition and rate of hemodynamic progression

AS severity quantitation is based on the degree of LVOT obstruction caused by progressive narrowing of the aortic valve orifice. Echocardiography with Doppler evaluation is the main modality for diagnosing AS. Traditionally, hemodynamic severity of AS has been described based on peak aortic jet velocity (V_{max}), MG, and AVA. According to the 2014 ACC/AHA guidelines, severe AS is defined as $V_{max} \geq 4.0$ m/s, MG ≥ 40 mmHg, and AVA < 1.0 cm^2 [24]. The rate of hemodynamic

progression in AS is highly variable. The average rate of progression was reported as increase in V_{max} by 0.3 m/s/year and MG by 7 mmHg/year and decrease in AVA by 0.1 cm^2/year [11]. Studies have shown that the strongest predictors of outcomes in AS were severity of the aortic valve obstruction. During a follow-up period of 2 years, progression of symptoms requiring AVR was about 80% for patients with V_{max} > 4.0 m/s vs. 35% with V_{max} of 3.0–4.0 m/s and 15% for patients with V_{max} < 3.0 m/s. MG and AVA, other parameters of stenosis severity, were also strong predictors of patient outcomes [25].

4. Discrepancies with echocardiographic criteria for grading AS

Echocardiography is the current standard modality for evaluating AS severity. However, challenges due to inconsistencies between measurements of the MG and the calculated AVA in patients with normal systolic function were noted (see **Figure 2**). This finding was attributed primarily to differences in stroke volume and flow across the aortic valve. While it seems possible that discrepancies can occur when the cardiac output is low from reduced LVEF, inconsistent measurements in patients with preserved LVEF were observed. Another potential explanation for the discrepancies was that effective valve area derived by Doppler echocardiography is often smaller than the anatomic valve area measured during cardiac catheterization or by planimetry or at autopsy. So while the initial guidelines for determining AS severity were based on invasive measurements (reflecting the anatomic valve area), echocardiographic Doppler measurements are currently used to make clinical decisions for AS patients still based on the original anatomic valve area criteria. Thus, based on AVA, it is possible that more patients may be categorized as having severe AS

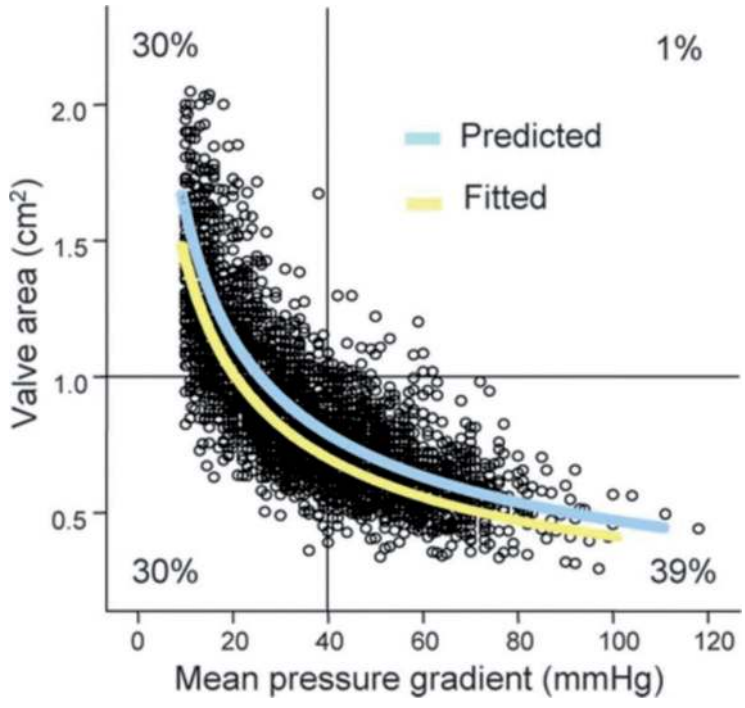

Figure 2.
Comparison of AVA vs. MG in AS patients with preserved LVEF. The predicted values from the Gorlin equation and the fitted curve of the study cohort are shown. The quadrants depict severe AS cutoff points based on the guidelines, and the percentages represent patients per quadrant. Thirty percent of the severe AS patients were diagnosed based on AVA, but not by MG [26].

relative to the peak flow velocity and MG. Therefore, some authors have suggested that AVA cutoff value for severe AS be changed to 0.8 cm^2 [26].

There are other potential etiologies of discrepant AVA and MG measurements in the setting of preserved LVEF which also need to be taken into consideration. First, technical errors need to be excluded. For example, LVOT diameter measurement may be inaccurate, and/or LVOT velocity time integral may be underestimated due to misplacement of the pulsed wave Doppler sample in the LVOT, leading to the underestimation of the stroke volume and the AVA. Second, patients with small body habitus and small LV dimensions could have lower stroke volume and lower transaortic gradient. Therefore, additional diagnostic studies such as dobutamine stress echocardiography (DSE), calcium scoring using multi-detector computed tomography (MDCT), and/or BNP may be necessary to corroborate AS severity and guide management strategy.

5. Hemodynamic classifications of AS

In patients with AVA < 1 cm^2, there are six flow-gradient patterns: NF/VHG, NF/HG, LF/HG, LF/LG with reduced LVEF, LF/LG with preserved LVEF, and NF/LG. VHG is defined as MG ≥ 60 mmHg, and HG is defined as MG ≥ 40 mmHg; stroke volume index (SVI) of normal flow is ≥35 ml/m^2. Low flow is defined as SVI < 35 ml/m^2. Low gradient is defined as MG < 40 mmHg. LF/LG AS with reduced LVEF is present when the gradient is low, the flow is low, and the LVEF is abnormal (<50%). LF/LG AS with preserved LVEF is present when the gradient is low and the flow is low but the LVEF is normal (>50%) (see **Table 1**).

5.1 High-gradient AS

Severe VHG AS (V_{max} ≥ 5.0 m/s) has significantly worse prognosis than severe HG AS (V_{max} ≥ 4.0 m/s) [3], so we acknowledge VHG AS as a separate entity from HG AS. However, most studies assessing AS severity using the new classification system combined NF/VHG and NF/HG as one entity under the subgroup of NF/HG. Thus, we will characterize these two groups together and highlight some of the relevant findings for VHG AS.

5.1.1 Normal flow/very high gradient or high gradient

NF/VHG AS pattern is defined as AVA < 1.0 cm^2, MG ≥ 60 mmHg, V_{max} ≥ 5.0 m/s, and LVEF ≥ 50% with SVI ≥ 35 ml/m^2. NF/HG AS is defined as MG ≥ 40 mmHg and V_{max} ≥ 4 m/s with the same criteria for AVA, LVEF, and SVI as NF/VHG. Patients with these two flow-gradient patterns are the most prevalent (up to 70%) of all the AS groups. These patients tend to have more severe valvular stenosis suggesting more prolonged exposure to the progressive disease process. Compared with the NF/LG group, there is preservation of LV longitudinal function. However, these patients have higher BNP level and lower cardiac-event free survival [27].

When evaluating AS severity, V_{max} is an important parameter which closely correlates with outcome. One study assessing the outcome of asymptomatic patients with very severe AS found that the higher the velocity, the lower the event-free survival with most patients experiencing some event within 3 years (see **Figure 3**). Patients with V_{max} ≥ 5 m/s were symptomatic at presentation. Furthermore, asymptomatic patients with V_{max} ≥ 5.5 m/s were highly likely to develop rapid onset of symptoms [3]. A landmark study evaluating the rate of hemodynamic progression and predictors of outcome in asymptomatic AS patients demonstrated that when V_{max} exceeds 4 m/s, virtually all patients become symptomatic in 5 years.

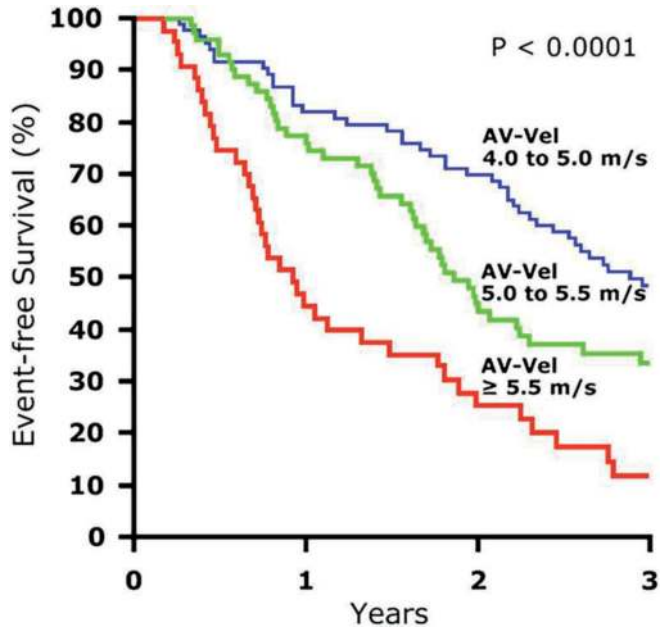

Figure 3.
Event-free survival with very severe AS. Kaplan-Meier estimates demonstrate that maximum aortic jet velocity closely correlates with outcome, with higher the velocity, the lower the event-free survival [3].

The velocity traditionally reflects the chronicity of the degenerative process. V_{max} between 3 and 4 m/s were also found to be not benign, and only 20% of patients remained asymptomatic over 5 years. Only when V_{max} was <3 m/s, there was an 85% chance that the patient will remain asymptomatic for 5 years [11] (see **Figure 4**).

MG is another well-recognized parameter for defining AS severity. One study assessed the prognostic impact of MG on all-cause mortality in severe AS with preserved LVEF. They found that MG > 60 mmHg at baseline was associated with greater risk of all-cause mortality than lower values, thereby justifying a separate hemodynamic classification. The higher MG also reflected the chronicity of the disease process [28] (see **Figure 5**).

AVA < 1.0 cm^2 also correlated with poor outcome compared to moderate or mild categories. More severe AVAs carried worse prognosis, and like V_{max} and MG, they reflected disease chronicity. While the rate of progression is highly variable, the often quoted number is 0.1 cm^2/year [29] (see **Figure 6**). However, when V_{max} was high or very high (4–6 m/s), there was no significant difference in the outcome based on the calculated AVA [3].

According to the current ACC/AHA guidelines, symptomatic NF/HG and NF/VHG severe AS patients have a class I indication for AVR. When asymptomatic, these AS subgroups are recommended to undergo further risk stratification.

5.1.2 Low flow/high gradient

This pattern of AS is defined as AVA < 1.0 cm^2, MG ≥ 40 mmHg, and LVEF ≥ 50% with SVI < 35 ml/m^2. The prevalence of this AS subtype is much less (8%) [30]. These patients have LV remodeling with reduced longitudinal function despite preserved LVEF. As a consequence, LV output is reduced with resultant lower than expected MG. LF/HG AS patients have shown to have high BNP, and their prognosis is similar or worse than those with NL/HG AS. When symptomatic, these patients have better survival with AVR [27, 31].

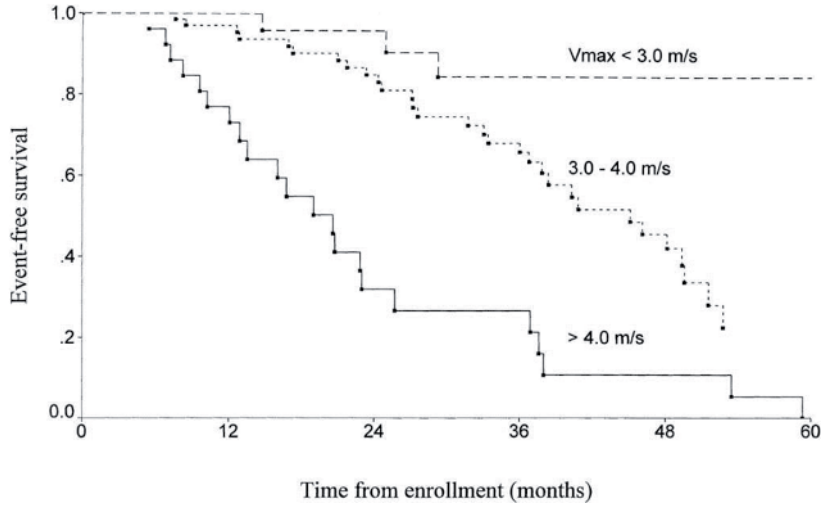

Figure 4.
Effect of V_{max} on outcomes in asymptomatic AS. Cox regression analysis demonstrating event-free survival in asymptomatic AS patients categorized by initial peak aortic jet velocity [11].

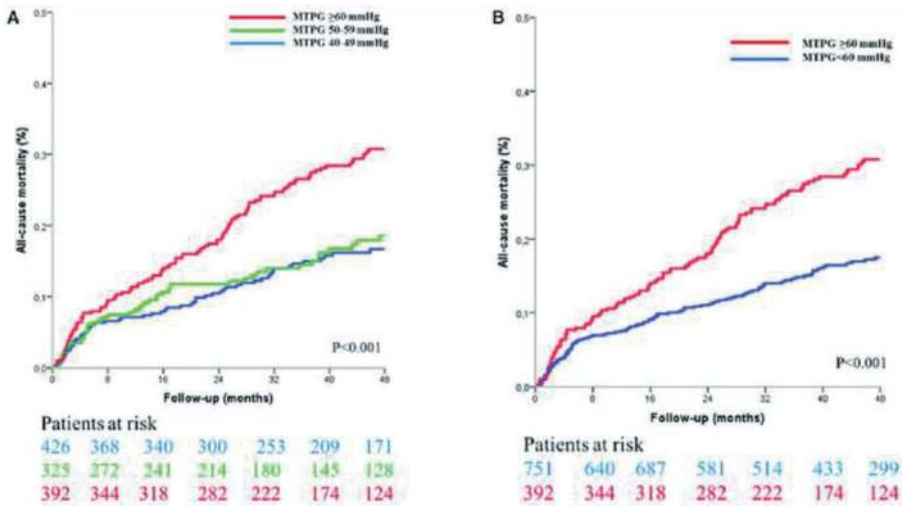

Figure 5.
Impact of MG on outcomes in severe AS. Kaplan-Meier estimates of survival based on MG [28].

5.2 Low-gradient AS

Three types of low-gradient severe AS have been described based on the LVEF and the flow state. LF/LG AS with reduced LVEF (<50%) is present when there is LV systolic dysfunction with reduced stroke volume in the setting of severe AS which results in decreased transvalvular velocity/gradient. If the LVEF is normal (≥50%), the stroke volume index (SVI) helps determine the presence of LF/LG AS with preserved LVEF (if the SVI is low, <35 ml/m^2) or NF/LG AS (if the SVI is normal, ≥35% ml/m^2) [32] (see **Table 2**).

5.2.1 Low flow/low gradient with reduced LVEF

This AS subtype, also known as "classical" LF/LG AS, is defined as AVA < 1.0 cm^2, MG < 40 mmHg, SVI < 35 ml/m^2, and LVEF < 50%. LF/LG AS with

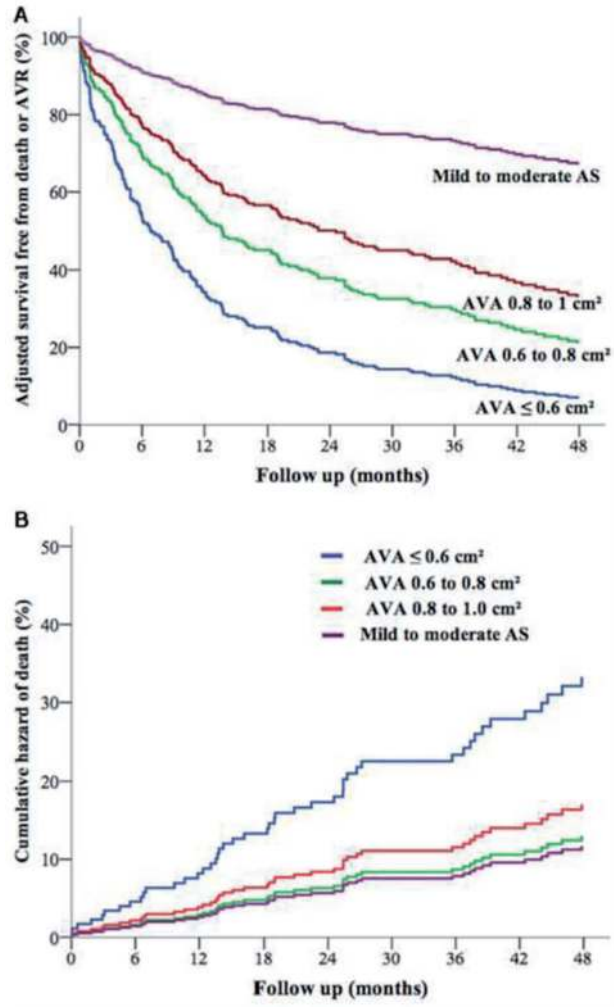

Figure 6.
(A) Adjusted event-free survival based on AVA. (B) Cumulative hazard of death based on AVA [29].

reduced LVEF accounts for about 5–10% of the AS population [33, 34] and has the worst outcome among all the AS categories [30, 33, 34]. The low flow state is usually associated with LV systolic dysfunction either from pressure overload due to the underlying severe AS or cardiomyopathy of another etiology.

In order to differentiate true-severe AS from pseudo-severe AS, low-dose DSE is the initial recommended study to determine whether there is normal flow reserve (an increase in stroke volume of >20%) or diminished flow reserve (see **Figure 7**). Patients with normal flow reserve may have true-severe AS (MG ≥ 40 mmHg with AVA < 1.0 cm^2 at any stage of DSE) which requires AVR or pseudo-severe AS (MG < 40 mmHg with AVA > 1.0 cm^2) where medical therapy is recommended [32, 35]. In patients where the increase in stroke volume with DSE is <20% but >15% and MG is <40 mmHg, the definitive diagnosis of AS severity may remain questionable. In this case, the projected AVA calculation using normal flow rate may be beneficial where a value <1.0 cm^2 is suggestive of true-severe AS [36] (see (Eq. (1)). However, if the stroke volume increase is <15%, further evaluation beyond DSE is often required, and calcium quantification of the aortic valve using MDCT is helpful in confirming the AS severity. The cutoff values for true-severe AS is >1200 AU in women and >2000 AU in men [37, 38].

Valvuloarterial impedance (Zva) is an index to evaluate global LV hemodynamic load using Doppler echocardiography (see Eq. (2)). Zva > 5 has been shown to predict adverse outcomes in patients with AS and LV dysfunction. Since AS is a disease of the elderly, in addition to valvular stenosis, vascular stiffness due to various factors including age and hypertension may be present. As a result, the LV may be subject to a double afterload, known as global LV afterload or Zva. In general, higher Zva is associated with worse outcome. However, since Zva is a flow-dependent parameter, this index may be less reliable in low flow states since small changes in stroke volume can produce large changes in Zva [39].

Low Gradient AS (MG < 40 mmHg, AVA < 1.0 cm2)	
	LF/LG AS with reduced LVEF LVEF < 50%, SVI < 35 ml/m^2
	LF/LG AS with preserved LVEF LVEF ≥ 50%, SVI < 35 ml/m^2
	NF/LG AS LVEF ≥ 50%, SVI ≥ 35 ml/m^2

AS, aortic valve stenosis; MG, mean transaortic gradient; AVA, aortic valve area; LF, low flow; LG, low gradient; NF, normal flow; LVEF, left ventricular ejection fraction; SVI, stroke volume index.

Table 2.
Subclassification of low gradient AS.

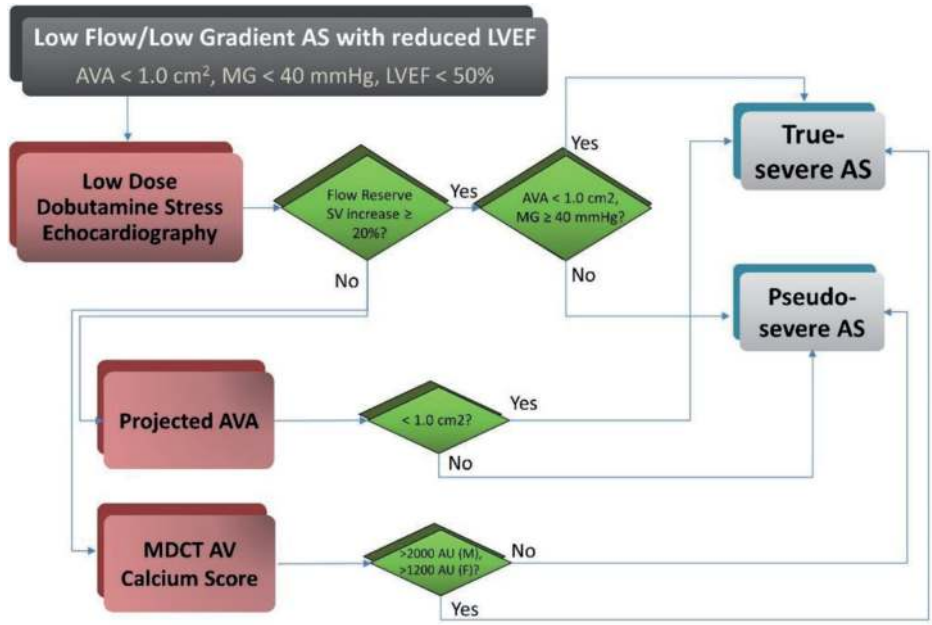

Figure 7.
Algorithm for diagnosing LF/LG AS with reduced LVEF. AS, aortic stenosis; AVA, aortic valve area; MG, mean gradient; LVEF, left ventricular ejection fraction; SV, stroke volume; AV, aortic valve; MDCT, multidetector computed tomography.

	Recommendation	Class
LF/LG AS with reduced LVEF (Stage D2)	AVR is reasonable in symptomatic patients with low LVEF, LF/LG severe AS with a DSE that shows MG ≥ 40mmHg with AVA < 1.0 cm^2 at any dobutamine dose.	**IIa**
LF/LG AS with preserved LVEF (Stage D3)	AVR is reasonable in symptomatic patients who have LF/LG severe AS who are normotensive and have an LVEF ≥ 50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms.	**IIa**

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185. AVR, aortic valve replacement, LF, low flow; LG, low gradient; AS, aortic stenosis; LVEF, left ventricular ejection fraction; DSE, dobutamine stress echocardiography; MG, mean gradient, AVA, aortic valve area.

Table 3.
Recommendations for aortic valve replacement in LF/LG AS.

Two-dimensional and three-dimensional transesophageal echocardiography may also be beneficial for confirming AS severity via direct visualization of the aortic valve anatomy and physiology.

In general, LF/LG AS has the worst prognosis compared to the other categories in part because the severity of AS is often under-recognized and surgical treatment is delayed. Patients with LF/LG AS with reduced LVEF have higher adverse event rates and mortality than LF/LG AS with preserved LVEF. The operative risk is also high in this AS subgroup. However, AVR has shown to have significant survival benefit compared to patients undergoing conservative management [40]. Furthermore, TAVR in LF/LG AS with reduced LVEF has demonstrated to have significant survival benefit compared with standard medical therapy in patients who are not suitable for surgery and similar outcomes compared with SAVR for patients at high surgical risk [41]. According to the ACC/AHA guidelines, true-severe LF/LG AS with reduced LVEF has a class IIa indication for AVR [42] (see **Table 3**).

5.2.2 Low flow/low gradient with preserved LVEF

LF/LG AS with preserved LVEF, also described as "paradoxical" LF/LG AS, is defined as AVA < 1.0 cm^2, AVA indexed < 0.6 cm^2/m^2, MG < 40 mmHg, SVI < 35 ml/m^2, and LVEF ≥ 50%. This AS pattern has generated much controversy among investigators. Studies have reported that low flow state is present in about 30% of AS patients with normal LVEF [31, 43–46]. This AS subgroup accounts for about 15–35% of the symptomatic and 5–10% of the asymptomatic AS patients [30]. The classic characteristics described with this AS subtype are small LV cavity size with marked concentric hypertrophy, myocardial fibrosis, restrictive diastolic physiology, reduced LV longitudinal systolic function, and increased global LV afterload resulting in reduced SVI and worse outcome [6, 31, 47]. Other factors associated with this pattern include women, older age, systemic and/or pulmonary hypertension, atrial fibrillation, mitral regurgitation, and right ventricular dysfunction [27, 46]. Some studies have shown that these patients have one of the worst prognoses as the disease severity is often under-recognized and surgery is delayed. This pattern has shown to have better outcomes than LF/LG AS with reduced LVEF but worse outcomes than moderate AS, HG AS, and NF/LG AS [31, 41, 48]. The likelihood of remaining alive in 3 years without AVR has been reported about five fold lower than normal flow state [43].

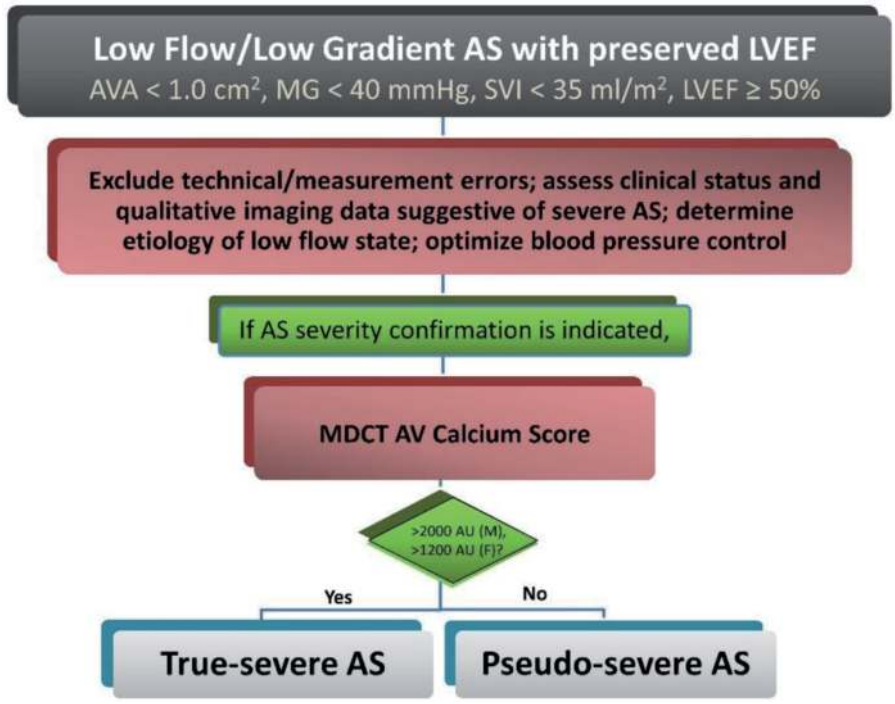

Figure 8.
Algorithm for diagnosing LF/LG AS with preserved LVEF. LF, low flow; LG, low gradient; AS, aortic stenosis; AVA, aortic valve area; MG, mean gradient; LVEF, left ventricular ejection fraction; SVI, stroke volume index; AV, aortic valve; MDCT, multi-detector computed tomography.

When evaluating patients with this AS entity, it is essential to first exclude potential technical errors which may affect the gradient, stroke volume, and AVA measurements. Next, an integrated approach assessing the different criteria to support severe AS needs to be evaluated. These parameters include clinical characteristics such as physical examination suggestive of severe AS, patient symptoms, and the presence of hypertension. Potential etiologies of low flow state need to be considered. Qualitative imaging analyses such as the presence of left ventricular hypertrophy and LV strain measurements should also be assessed. Once LF/LG AS with preserved LVEF status is confirmed, quantitation of aortic valve calcification using MDCT may be helpful in differentiating true-severe vs. pseudo-severe AS [35, 49] (see **Figure 8**). One small study showed that low-dose DSE may be useful in confirming the diagnosis with this entity [50].

According to the ACC/AHA guidelines, LF/LG AS with preserved LVEF has a class IIa indication for AVR, if clinical, anatomic, and hemodynamic data support that the patient's symptom is from the obstructive pathophysiology of the aortic valve [42] (see **Table 3**). One randomized trial data showed significant survival benefit after TAVR compared to standard medical treatment or similar clinical outcomes vs. SAVR [41]. In patients with greater degree of LV myocardial fibrosis, more advanced stage of diastolic dysfunction and low SVI demonstrated worse outcomes after TAVR [51, 52].

In contrast to the findings described above, some other investigators have shown differing results for this AS entity. In one prospective study with a large number of patients with asymptomatic AS, there was no difference between the moderate stenosis and the low-gradient "severe" AS groups in terms of valve-associated events, major cardiovascular events, or cardiac death, even when the groups were subcategorized into low flow and normal flow states [53].

Another large study demonstrated that patients with LF/LG AS with preserved LVEF had better spontaneous survival than the patients with HG severe AS, and the results are unaffected by flow states. Furthermore, the patients with LF/LG AS with preserved LVEF progressed to develop HG AS over time, and in all patients who showed a reduction in transvalvular gradients over time, this decrease was associated with reduction in LVEF [54]. Another study showed that patients with severe LF/LG AS with preserved LVEF had similar outcomes as patients with mild to moderate AS, and there was no significant benefit of AVR in this group [55]. However, a comparison of two studies by Hachicha et al. [31] and Jander et al. [53] showed that there were some differences between the study group findings which may, at least in part, have contributed to the differing outcomes. Some investigators have proposed for reducing the AVA cutoff value for severe AS closer to ≤ 0.8 cm^2 to avoid overestimation of AS severity [56].

5.2.3 Normal flow/low gradient

This AS pattern is defined as AVA < 1.0 cm^2, AVA indexed < 0.6 cm^2, MG < 40 mmHg, and LVEF ≥ 50% with SVI ≥ 35 ml/m^2. NF/LG AS has shown to be present in about one third of AS patients [30], and some studies have suggested that this AS pattern may be due to marked reduction in transaortic gradient from systemic hypertension and decreased aortic compliance [57, 58]. Patients with NL/LG AS are reported to have less severe disease than the other AS categories with lower BNP and preserved LV longitudinal function [35]. In terms of diagnosis, technical measurement errors need to be excluded, and aortic valve calcium scoring using MDCT may be beneficial to further determine the AS severity [38]. According to the 2017 European Association of Cardiovascular Imaging and the American Society of Echocardiography Recommendations, however, this entity is considered to be due to measurement errors or the consequence of inconsistent cutoff values for transaortic velocity/gradient and AVA [35]. Some studies have supported this thought as patients in the NF/LG AS subgroup demonstrated the same outcome as patients with moderate AS [59].

There are no particular recommendations for this subgroup in the current guidelines, and AVR should only be considered in symptomatic patients with confirmed severe AS. One study showed survival benefit in these patients [43], while another study showed no difference in survival in patients who underwent early AVR compared to conservative management [60].

Projected AVA calculation

$$\text{Projected AVA} = \text{AVArest} + \left(\frac{\Delta\,\text{AVA}}{\Delta\,\boldsymbol{Q}} \right) * (\mathbf{250} - \boldsymbol{Q}\text{rest})$$

$$\Delta\ \text{AVA} = \text{AVApeak} - \text{AVArest} \ = \ \text{Change in AVA at rest and at peak DSE}$$

$$\Delta\ \text{Q} = \text{Qpeak} - \text{Qrest} \ = \ \text{Change in } \boldsymbol{Q} \text{ at rest and at peak DSE} \qquad (1)$$

Projected AVA at a normal flow rate (250 ml/s) <1.0 cm^2 suggests severe AS.

AVArest, aortic valve area at rest; DSE, dobutamine stress echocardiography; AVApeak, aortic valve area at peak; *Q*rest, stroke volume at rest; *Q*peak, stroke volume at peak DSE.

Valvuloarterial impedance calculation

$$Zva = \frac{\text{Systemic Arterial Pressure + Mean Pressure Gradient}}{\text{Stroke Volume Index}}$$

Zva = Valvuloarterial Impedence (2)

6. Conclusions

The different hemodynamic categories of severe AS have shown to have varying clinical outcomes. Low flow state has exhibited the worst prognosis due to intrinsic myocardial dysfunction and/or under-recognition of the disease severity resulting in inappropriate delay in AVR. Low-gradient AS with low flow state is of particular challenge for clinical decision-making, especially when differentiating true-severe AS (where AVR may be beneficial) vs. pseudo-severe AS (where conservative medical management is appropriate). In LF/LG AS with reduced LVEF, DSE is beneficial for the confirmation of AS severity and risk stratification. In the setting of partial or no flow reserve, projected AVA and/or calcium scoring with MDCT may be useful to guide management. LF/LG AS with preserved LVEF is an entity where the natural history and the pathophysiology are not well understood. There has been much controversy and differing schools of thought around this AS subgroup. Numerous studies have shown that LF/LG AS with preserved LVEF is associated with poor prognosis, and therefore, careful evaluation and identification of these patients are necessary to ensure proper management. Calcium quantification using MDCT has shown to be the preferred technique for confirming AS severity with this subgroup. However, other investigators have reported that this AS entity represents moderate AS with no significant difference in outcomes between the groups. These discrepant findings may be resolved based on more randomized studies with large cohorts and with the application of more advanced diagnostic imaging techniques capable of overcoming the limitations of the currently available technology to better assess AS severity. In symptomatic high-gradient severe AS, regardless of the flow state, AVR is the only treatment option that has demonstrated to improve symptoms and survival. In asymptomatic high-gradient severe AS, regardless of the flow state, the current guidelines recommend watchful waiting and conservative management, although controversy exists about the optimal timing of intervention.

Over the years, the operative risk for SAVR for severe AS has significantly decreased, and TAVR has emerged as a promising alternative treatment for these patients with different operative risk profiles—high, intermediate, and more recently low risk. Recent data have supported that TAVR is superior or noninferior to SAVR in the treatment of severe AS and long-term follow-up assessment will better validate the true comparison between the two approaches and determine the optimal treatment strategy. As the TAVR technology continues to advance, the next generations of bioprostheses will be introduced which may further improve outcomes. Therefore, it is vital to accurately diagnose AS severity and identify those individuals who may benefit from AVR in a timely manner to optimize patient care and clinical outcomes.

Conflict of interest

None.

Author details

Susan Kwon and Aasha Gopal*
St. Francis Hospital, Roslyn, New York, USA

*Address all correspondence to: aasha.gopal@gmail.com

IntechOpen

References

[1] Nkomo VT et al. Burden of valvular heart diseases: A population-based study. Lancet. 2006;**368**(9540):1005-1011

[2] Otto CM, Prendergast B. Aortic-valve stenosis—From patients at risk to severe valve obstruction. The New England Journal of Medicine. 2014;**371**(8):744-756

[3] Rosenhek R et al. Natural history of very severe aortic stenosis. Circulation. 2010;**121**(1):151-156

[4] Pai RG et al. Malignant natural history of asymptomatic severe aortic stenosis: Benefit of aortic valve replacement. The Annals of Thoracic Surgery. 2006;**82**(6):2116-2122

[5] Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;**63**(22):2438-2488

[6] Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: Implications for diagnosis and treatment. European Heart Journal. 2010;**31**(3):281-289

[7] Rosenhek R et al. Predictors of outcome in severe, asymptomatic aortic stenosis. The New England Journal of Medicine. 2000;**343**(9):611-617

[8] Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;**38**(1 Suppl):61-67

[9] Braunwald E. On the natural history of severe aortic stenosis. Journal of the American College of Cardiology. 1990;**15**(5):1018-1020

[10] Nessmith MG et al. Usefulness of an elevated B-type natriuretic peptide in predicting survival in patients with aortic stenosis treated without surgery. The American Journal of Cardiology. 2005;**96**(10):1445-1448

[11] Otto CM et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997;**95**(9):2262-2270

[12] Pellikka PA et al. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. Journal of the American College of Cardiology. 1990;**15**(5):1012-1017

[13] Pierard S et al. Impact of preoperative symptoms on postoperative survival in severe aortic stenosis: Implications for the timing of surgery. The Annals of Thoracic Surgery. 2014;**97**(3):803-809

[14] Halkos ME et al. Aortic valve replacement for aortic stenosis in patients with left ventricular dysfunction. The Annals of Thoracic Surgery. 2009;**88**(3):746-751

[15] Azevedo CF et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. Journal of the American College of Cardiology. 2010;**56**(4):278-287

[16] Weidemann F et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation. 2009;**120**(7):577-584

[17] Rosenhek R, Maurer G, Baumgartner H. Should early elective surgery be performed in patients with severe but asymptomatic aortic stenosis? European Heart Journal. 2002;**23**(18):1417-1421

[18] Leon MB et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England Journal of Medicine. 2010;**363**(17):1597-1607

[19] Popma JJ et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. Journal of the American College of Cardiology. 2014;**63**(19):1972-1981

[20] Smith CR et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England Journal of Medicine. 2011;**364**(23):2187-2198

[21] Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. The New England Journal of Medicine. 2014;**371**(10):967-968

[22] Reardon MJ et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. The New England Journal of Medicine. 2017;**376**(14):1321-1331

[23] Mack MJ et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. The New England Journal of Medicine. 2 May 2019;**380**(18):1695-1705

[24] Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;**129**(23):e521-e643

[25] Vahanian A, Otto CM. Risk stratification of patients with aortic stenosis. European Heart Journal. 2010;**31**(4):416-423

[26] Minners J et al. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. European Heart Journal. 2008;**29**(8):1043-1048

[27] Lancellotti P, Davin L, Dulgheru R. Aortic stenosis grading and outcome: New categories, new therapeutic challenges. JACC: Cardiovascular Imaging. 2016;**9**(11):1264-1266

[28] Bohbot Y et al. Impact of mean transaortic pressure gradient on long-term outcome in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Journal of the American Heart Association. 2017;**6**(6):e005850. DOI: 10.1161/JAHA 117.005850

[29] Marechaux S et al. Prognostic value of aortic valve area by Doppler echocardiography in patients with severe asymptomatic aortic stenosis. Journal of the American Heart Association. 2016;**5**(5):e003146. DOI: 10.1161/JAHA. 115.003146

[30] Lancellotti P. Grading aortic stenosis severity when the flow modifies the gradientvalve area correlation. Cardiovascular Diagnosis and Therapy. 2012;**2**(1):6-9

[31] Hachicha Z et al. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;**115**(22):2856-2864

[32] Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. Journal of the American College of Cardiology. 2012;**60**(19):1845-1853

[33] Connolly HM et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. Circulation. 1997;**95**(10):2395-2400

[34] Connolly HM et al. Severe aortic stenosis with low transvalvular

gradient and severe left ventricular dysfunction: Result of aortic valve replacement in 52 patients. Circulation. 2000;**101**(16):1940-1946

[35] Baumgartner HC et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. European Heart Journal Cardiovascular Imaging. 2017;**18**(3):254-275

[36] Clavel MA et al. Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: The multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. Journal of the American Society of Echocardiography. 2010;**23**(4):380-386

[37] Cueff C et al. Measurement of aortic valve calcification using multislice computed tomography: Correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011;**97**(9):721-726

[38] Clavel MA et al. The complex nature of discordant severe calcified aortic valve disease grading: New insights from combined Doppler echocardiographic and computed tomographic study. Journal of the American College of Cardiology. 2013;**62**(24):2329-2338

[39] Lancellotti P, Magne J. Valvuloarterial impedance in aortic stenosis: Look at the load, but do not forget the flow. European Journal of Echocardiography. 2011;**12**(5):354-357

[40] Tribouilloy C et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. Journal of the American College of Cardiology. 2009;**53**(20):1865-1873

[41] Herrmann HC et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: A Placement of Aortic transcatheter Valves (PARTNER) trial analysis. Circulation. 2013;**127**(23):2316-2326

[42] Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;**63**(22):e57-e185

[43] Lancellotti P et al. Clinical outcome in asymptomatic severe aortic stenosis: Insights from the new proposed aortic stenosis grading classification. Journal of the American College of Cardiology. 2012;**59**(3):235-243

[44] Mohty D et al. Outcome and impact of surgery in paradoxical low-flow, low-gradient severe aortic stenosis and preserved left ventricular ejection fraction: A cardiac catheterization study. Circulation. 2013;**128**(11 Suppl 1):S235-S242

[45] Ozkan A et al. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. Circulation. 2013;**128**(6):622-631

[46] Eleid MF et al. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: Clinical characteristics and predictors of survival. Circulation. 2013;**128**(16):1781-1789

[47] Adda J et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction

as assessed by speckle-tracking echocardiography: A multicenter study. Circulation. Cardiovascular Imaging. 2012;**5**(1):27-35

[48] Clavel MA et al. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. Journal of the American College of Cardiology. 2012;**60**(14):1259-1267

[49] Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. European Heart Journal. 2016;**37**(34):2645-2657

[50] Clavel MA et al. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. JACC: Cardiovascular Imaging. 2013;**6**(2):175-183

[51] Le Ven F et al. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. Journal of the American College of Cardiology. 2013;**62**(9):782-788

[52] Herrmann S et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. Journal of the American College of Cardiology. 2011;**58**(4):402-412

[53] Jander N et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation. 2011;**123**(8):887-895

[54] Maes F et al. Natural history of paradoxical low-gradient severe aortic stenosis. Circulation. Cardiovascular Imaging. 2014;**7**(4):714-722

[55] Tribouilloy C et al. Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: Characteristics, outcome, and implications for surgery. Journal of the American College of Cardiology. 2015;**65**(1):55-66

[56] Zoghbi WA. Low-gradient "severe" aortic stenosis with normal systolic function: Time to refine the guidelines? Circulation. 2011;**123**(8):838-840

[57] Eleid MF et al. Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction. Circulation. 2013;**128**(12):1349-1353

[58] Kadem L et al. Impact of systemic hypertension on the assessment of aortic stenosis. Heart. 2005;**91**(3):354-361

[59] Mehrotra P et al. Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis. European Heart Journal. 2013;**34**(25):1906-1914

[60] Kang DH et al. Watchful observation versus early aortic valve replacement for symptomatic patients with normal flow, low-gradient severe aortic stenosis. Heart. 2015;**101**(17):1375-1381