

Diagnosis and management of patients with asymptomatic severe aortic stenosis

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Abstract

Aortic stenosis (AS) is a disease that progresses slowly for years without symptoms, so patients need to be carefully managed with appropriate follow up and referred for aortic valve replacement in a timely manner. Development of symptoms is a clear indication for aortic valve intervention

in patients with severe AS. The decision for early surgery in patients with asymptomatic severe AS is more complex. In this review, we discuss how to identify high-risk patients with asymptomatic severe AS who may benefit from early surgery.

Key words: Aortic stenosis; Asymptomatic; Diagnosis; Management; Treatment

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Core tip: We focused on how to identify high-risk patients in asymptomatic aortic stenosis. Revised American Heart Association/American College of Cardiology guidelines and diagnostic testing for appropriate clinical decision making are discussed in this article.

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INTRODUCTION

As a result of the aging population, aortic stenosis (AS) is currently one of the most common valvular heart diseases to need surgical intervention. AS is a slowly progressive chronic condition, but once a patient becomes symptomatic, the prognosis is dismal. Although percutaneous valve technology is now approved for high-risk patients with symptomatic AS, clinical management of asymptomatic patients with severe AS is still difficult. Assessment of symptoms in sedentary elderly patients with severe AS is often challenging. It is common for patients to have nonspecific symptoms such as shortness of breath or general feelings of weakness that can be

explained by many reasons other than cardiac diseases. Advances in multiple modality imaging provide additional objective information about subtle functional deterioration of the left ventricle (LV), myocardial tissue damage, and the amount of the valve calcification. Existing and new parameters are investigated to improve the clinical decision-making process.

In this review, we focus on recent advances in diagnostic methods for assessment of AS and discuss how to implement these methods in current clinical practice as it relates to the management of patients with asymptomatic severe AS.

PATHOPHYSIOLOGY AND HEMODYNAMICS OF AS

A normal aortic valve is tricuspid and a normal valve opening area is 3 to 4 cm². Progression from aortic valve sclerosis to AS is reported to be 9% per 5 years^[1]. There is some evidence to suggest that NOTCH 1 genetic mutations and specific lipoprotein polymorphism is associated with congenital AS and valve calcification^[2]. In AS, it has been reported that an average rate of increase in mean gradient is 7 to 8 mmHg/year; in maximum velocity, 0.2 to 0.4 m/s per year; and in a decrease in valve area, 0.1 to 0.15 cm²/year^[3-6]. Hemodynamic progression of AS is gradual and linear, though there is variability and some patients present with rapid progression. Presence of aortic valve calcification, coronary artery disease, advanced age, renal impairment, and baseline AS severity are risk factors for rapid progression^[4,7-9].

The hemodynamic progression of AS lead to LV hypertrophy (LVH) as a compensation mechanism of the heart. Morphological changes such as increasing muscle fiber thickness, collagen volume, and interstitial fibrosis occur in AS patients^[10]. These changes result in LV diastolic and systolic dysfunction^[11]. LV mass regression starts soon after aortic valve replacement (AVR) and may continue through another 8 years postoperatively, while diastolic dysfunction persists up to 2 years due to the relatively increased amount of fibrotic tissue in the myocardium^[12-14]. These results may encourage AVR before the fibrotic change becomes too substantial or irreversible to advance postoperative recovery. Thus, the amount of myocardial structural change in AS can be a good parameter to define the severity of AS, and the new imaging technique gains greater prominence to determine the timing of surgical intervention in asymptomatic severe AS^[15].

When the valve area is decreased to one-fourth of the normal valve area (0.75-1.00 cm²), in general, patients develop symptoms, although there is high inter-individual variability. A fundamental principle of fluid dynamics is that flow velocity within the conduit depends on volumetric flow rate. Patients with normal LVEF (LV ejection fraction) and normal flow will generally have a mean gradient > 40 mmHg in the setting of severe AS. However, recent studies have identified a

new entity, termed "paradoxical low-gradient severe AS", where the stroke volume is reduced in the setting of increased afterload and concentric LVH, resulting in a low gradient despite severe AS in the setting of normal LVEF. Recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines have recognized this entity and have developed guidelines for management of this new group of AS patients.

DEFINITION OF AS

AHA/ACC guidelines for the management of patients with valvular heart disease, which was revised in 2014, has a major change for the staging of AS (Table 1)^[16].

It should be noted that the stage D3 definition is based on a relatively new concept related to the progression of AS. Specifically, low-flow/low-gradient AS with preserved EF represents a more advanced stage of AS with severe concentric hypertrophy, high peripheral arterial pressure, and low systemic arterial compliance^[17-19]. Valvulo-arterial impedance (Zva) calculated as shown below was introduced as a global hemodynamic load on the LV in AS^[17,20,21]. $Zva = (\text{systolic blood pressure} + \text{mean gradient of aortic valve})/\text{stroke volume index}$.

More importantly, low-flow/low-gradient severe AS is reported to have a poorer prognosis without surgical intervention in some studies^[17,22,23], while other studies report a better prognosis-similar to the prognosis of patients with moderate AS^[24-26]. Nevertheless, the majority of evidence is in favor of the new entity termed "paradoxical low-gradient AS", in which LVEF is preserved yet the mean aortic valve gradient is low due to low stroke volume.

This condition must be diagnosed with utmost caution, avoiding measurement errors and, in some cases, establishing additional diagnostic methods such as cardiac catheterization or other imaging studies, including magnetic resonance imaging (MRI) and computed tomographic (CT) scans.

Current ACC/AHA guidelines put much more focus on velocity/pressure gradient findings than on aortic valve area (AVA) given that prior natural history studies show their prognostic importance. Namely, aortic velocity (> 4 m/s) is reported to be one of the most important factors associated with a higher event rate in AS^[4,5,27]. Asymptomatic patients with very severe AS with a $V_{max} \geq 5$ m/s or mean gradient ≥ 60 mmHg have an even worse event-free survival^[28].

DIAGNOSTIC TESTING

Echocardiography for diagnosis of severe AS

Two-dimensional/Doppler echocardiography plays a fundamental role in the diagnosis of AS. It is important to examine the etiology of AS, visual severity of valve calcification, position of the coronary artery orifice, concomitant myocardial disease, wall motion asynergy, and other valvular heart diseases with echocardiography.

Table 1 Stages of aortic stenosis on the basis of American College of Cardiology/American Heart Association recommendations

		Hemodynamics	LV Function	AVA	Aortic valve
A	At risk of AS	$V_{\max} < 2$ m/s	Normal EF	-	Bicuspid, sclerosis
B	Progressive AS	Mild AS: $V_{\max} < 2.0$ - 2.9 m/s or mean $\Delta P < 20$ mmHg Moderate AS: $V_{\max} > 3.0$ - 3.9 m/s or mean $\Delta P > 20$ - 39 mmHg	Normal EF Early diastolic dysfunction	-	Mild to moderate calcification Reduction in motion Commissural fusion
C1	Asymptomatic severe AS	$V_{\max} \geq 4$ m/s or mean $\Delta P \geq 40$ mmHg	Normal EF Diastolic dysfunction	≤ 1.0 cm ² or ≤ 0.6 cm ² /m ²	Severe calcification Severely reduced opening
C2	Asymptomatic severe AS with LV dysfunction	$V_{\max} \geq 4$ m/s or mean $\Delta P \geq 40$ mmHg	EF < 50%	≤ 1.0 cm ² or ≤ 0.6 cm ² /m ²	Severe calcification Severely reduced opening
D1	Symptomatic severe high-gradient AS	$V_{\max} \geq 4$ m/s or mean $\Delta P \geq 40$ mmHg	EF normal or decreased diastolic dysfunction	≤ 1.0 cm ² or ≤ 0.6 cm ² /m ² Larger with AR/MR	Severe calcification Severely reduced opening
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	$V_{\max} < 4$ m/s or mean $\Delta P < 40$ mmHg DOB stress shows $V_{\max} > 4$ m/s and AVA ≤ 1.0 cm ²	EF < 50% diastolic dysfunction	≤ 1.0 cm ²	Severe calcification Severely reduced opening
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	$V_{\max} < 4$ m/s or mean $\Delta P < 40$ mmHg Stroke volume index < 35 mL/m ²	EF $\geq 50\%$ Small LV chamber Restrictive diastolic filling	≤ 1.0 cm ² or ≤ 0.6 cm ² /m ²	Severe calcification Severely reduced opening

Modified from Nishimura *et al*^[16] with permission. ACC/AHA: American College of Cardiology/American Heart Association; AR: Aortic regurgitation; AS: Aortic stenosis; AVA: Aortic valve area; EF: Ejection fraction; LV: Left ventricular; MR: Mitral regurgitation; ΔP : Pressure gradient; V_{\max} : Maximum aortic velocity.

Echocardiography can provide systolic and diastolic functions. All parameters referred to in guidelines are available by echocardiography, which sometimes needs careful data interpretation while recognizing limitations.

An important consideration in echocardiography is to detect the highest peak aortic flow velocity using multiple transducer positions (the suprasternal window and right parasternal window with right decubitus position should be used in addition to the apical window). The Pedoff probe, which has a high signal to noise ratio, is ideal to detect the highest velocity. This requires advanced operator skill and, therefore, missing the highest velocity in AS is one of the causes of underestimation of the gradient.

The pressure gradient is calculated according to the modified Bernoulli equation; the pressure gradient = $4 \times v^2$. However, if there is an increased velocity (> 1.5 m/s) at the LV outflow tract (LVOT) by septal thickening or by systolic anterior motion of the mitral valve, this simplified equation is less reliable. In those cases, it is recommended that the corrected peak to peak gradient should be used^[29].

AVA is calculated by a continuity equation. Measurement of the LVOT size for stroke volume calculation is the second possible error for diagnostic severity. American Society of Echocardiography guidelines recommend the measurement at the same position of the pulse wave sample volume, specifically 0.5 to 1 cm below the aortic annulus^[29]. Accurate measurement of LVOT diameter is critical, as the continuity method requires squaring of this measurement. Even an error of a few millimeters in this measurement can lead to large differences in the

calculated valve area.

Additionally, appropriate position of the pulse-wave Doppler signal to avoid flow acceleration by calcified valve or outflow obstruction is important. Overestimation or underestimation of stroke volume can lead to an unreliable calculation of AVA. In some patients, one may also encounter dynamic LVOT obstruction with flow acceleration in the LVOT. In these patients, one must calculate stroke volume either by two-dimensional or three-dimensional volumetric methods. One can also use RVOT diameter and Doppler signals at the right ventricular outflow tract to calculate stroke volume.

AVA can also be measured by planimetry, both by transthoracic echocardiography and transesophageal echocardiography^[30]. The planimetry method has its own limitations. Shadowing by calcification interferes with the visualization of the valve edge. The anatomical orifice area can be measured larger than the effective orifice area. Nonplanar structures of the valve may cause difficulty in reliable measurement, which is improved by real-time three-dimensional echocardiography^[31]. With careful attention to these limitations, planimetry can be considered an alternative/complimentary measure when Doppler measurements are not appropriate.

A low-dose dobutamine stress echocardiography is performed to diagnose true or pseudo AS in low-gradient, reduced EF patients (though usually symptomatic, patients rarely present with low LVEF and gradient without any symptom). In addition, low-dose dobutamine echocardiography can identify high-risk patients who do not have contractile reserve, *i.e.*, an increase in stroke volume $\geq 20\%$. Loss of contractile reserve suggests a

patient may have other myocardial disease or advanced stages of severe AS. A maximum velocity ≥ 4.0 m/s with AVA ≤ 1.0 cm² at any flow rate during dobutamine stress echocardiography is diagnosed as true severe AS^[16,29]. Pseudo AS would show an increase of valve area to > 1.0 cm². Although suggested, evidence for the use of dobutamine stress evaluation of low-flow/low-gradient AS with preserved EF ("paradoxical low-gradient severe AS") to diagnose true/pseudo AS is limited.

Diastolic dysfunction is an important parameter in the evaluation of AS. Worsening of diastolic function is related to age and other comorbidities, such as hypertension, that are not uncommon in the elderly. It has been reported by Park *et al.*^[32] that echocardiographic markers of diastolic dysfunction, such as increased E/e' and left atrial volume index, are associated with dyspnea in severe AS patients. Increased E/e' (> 15) has been shown to predict survival in both asymptomatic and symptomatic patients with AS (adjusted mortality risk = 2.34; 95%CI: 1.27-4.33)^[33]. Although echocardiographic measures of diastolic dysfunction are markers of worse AS, current guidelines do not support its use in surgical decision making in patients with either symptomatic or asymptomatic AS.

Recent advances in echocardiography led to the development of newer methods to detect subtle changes in LV function beyond EF. Specifically, two-dimensional speckle-tracking echocardiography has been used in numerous research studies to detect early systolic functional deterioration in cardiomyopathies, including amyloidosis and hypertrophic cardiomyopathy. Global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography is decreased in severe AS and can be used as a prognostic measure. Kearney *et al.*^[34] reported that decreased GLS ($> -15\%$) in asymptomatic severe AS with preserved EF had poor survival when compared to patients with GLS $\leq -15\%$, and GLS was a predictor of all-cause mortality (HR = 1.42; 95%CI: 1.27-1.59). Using echocardiography, van Dalen *et al.*^[35] and Staron *et al.*^[36] reported that increased apical rotation is more common in AS patients than control patients. In general, worsening systolic longitudinal motion, apical rotation, and diastolic untwisting working in concert are manifestations of progressive AS. Further research studies and standardization of analyzing software are necessary to incorporate these measurements into current clinical practice, specifically their role in surgical decision making for patients with asymptomatic severe AS.

CT calcification score

Aortic valve calcification (AVC) is a prognostic factor in asymptomatic AS. Rosenhek *et al.*^[27] evaluated the degree of AVC using echocardiography and showed moderate and severe AVC related to future death or development of symptoms (RR = 5.2; 95%CI: 2.4-13.5). However, the definition of the degree of AVC by echocardiography has not been established. Therefore, evaluation of AVC by echocardiography is still a qualitative and subjective measure that is dependent on the echocardiographer's experience. A cardiac CT scan can provide quantitative

measure of AVC, and > 1000 Agaston units can be considered severe calcification^[16,37]. Currently, a cardiac CT scan can be used as a complementary method for the diagnosis and management of AS^[16]. When it is difficult to judge the severity of AS due to discordant measurements in echocardiography or a possible paradoxical low-flow/low-gradient AS, CT imaging can help to provide the calcium score, which relates to stenosis severity and prognosis^[38,39]. Due to the recent rapid development of transcatheter aortic valve replacement (TAVR) procedures, the cardiac CT scan has emerged as a key imaging modality not only to assess aortic valve and root calcification, but also for precise measurement of the aortic annulus and peripheral arteries^[40-42]. Whether or not three-dimensional LVOT measurements by CT imaging should replace echocardiography in order to resolve the measurement error issue is still uncertain, and warrants further research^[43,44].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has the advantage of providing more accurate anatomical and hemodynamic information, LV mass, and stroke volume than echocardiography. In addition, cardiac MRI with gadolinium contrast can provide information about fibrosis or collagen deposition of the myocardium, which is a consequence of long-term exposure to substantial afterload. The presence or absence of myocardial fibrosis in any cardiac disease is an important prognostic factor^[45-48]. Dweck *et al.*^[49] performed contrast-enhanced cardiac MRI in 143 AS patients, and the reported late gadolinium enhancement in the mid wall was a predictor of all-cause mortality (HR = 8.59; 95%CI: 1.97-37.38). Further research using more sensitive methods, *i.e.*, T1 mapping, to detect myocardial fibrosis in AS patients, as well as prognostic studies linking fibrosis to better outcomes, are warranted before MRI can be used in routine clinical practice for the management of patients with AS^[50].

Biomarkers in AS

Brain natriuretic peptide (BNP) is thought to be a good marker of increased wall stress in the myocardium, thus BNP increases with age, the presence of hypertension, valvular heart disease, and other myocardial diseases. It has been reported that BNP increases along with the severity of AS, but considerable overlap between the groups has also been observed. Bergler-Klein *et al.*^[51] reported that asymptomatic severe AS patients whose plasma BNP was < 130 pg/mL rarely developed symptoms for 6 to 9 mo. Another study showed that a BNP ≥ 300 pg/mL was a poor prognostic factor in medically followed severe AS patients who were both symptomatic and asymptomatic^[33]. More recently, Clavel *et al.*^[52] reported that moderate/severe asymptomatic AS patients with BNP clinical activation and an elevated BNP greater than the upper normal range of the same age/sex have a higher rate of mortality (HR = 2.35; 95%CI: 1.57-3.56). Recently published research is summarized in Table 2. Disadvantages of BNP include

Table 2 High-risk patients predicted from brain natriuretic peptide level

Source	BNP cut-off value	Results	Enrolled patients
Bergler-Klein <i>et al</i> ^[51]	BNP 130 pg/mL	BNP < 130 pg/mL (<i>n</i> = 25) had better symptom-free survival (<i>P</i> < 0.001)	Asymptomatic severe AS, EF ≥ 50% (<i>n</i> = 43)
Biner <i>et al</i> ^[33]	BNP 300 pg/mL	Combined use of BNP > 300 pg/mL and E/e' > 15 predicted 1-yr mortality (hazard ratio = 2.59; 95%CI: 1.21-5.55, <i>P</i> = 0.014)	Severe AS, symptomatic and asymptomatic, any EF included (<i>n</i> = 79)
Berger-Klein <i>et al</i> ^[54]	BNP 550 pg/mL	BNP ≥ 550 pg/mL showed poorer survival both in medically and surgically treated groups	Indexed effective orifice area ≤ 0.6 cm ² /m ² with low-flow/low-gradient AS; symptomatic and asymptomatic, with EF ≤ 40% (<i>n</i> = 69)
Clavel <i>et al</i> ^[52]	BNP ratio: Measured BNP/maximal-normal-BNP for age and sex	Higher BNP ratio showed worse mortality in asymptomatic patients with preserved EF (hazard ratio = 2.35; 95%CI: 1.57-3.56, <i>P</i> < 0.0001)	Total, moderate or severe AS, any EF (<i>n</i> = 1953) Asymptomatic, with EF > 50% (<i>n</i> = 565)

AS: Aortic stenosis; BNP: Brain natriuretic peptide; EF: Ejection fraction.

that fact that it is not disease-specific, and BNP levels vary even in the same patient according to physical activities and loading conditions. Therefore, a single value of BNP may not be helpful in surgical decision making in asymptomatic severe AS patients. However, serial measures and rising levels of BNP can be used for surgical decision making in asymptomatic severe AS patients, as proposed by European Society of Cardiology (ESC) guidelines^[53].

Stress testing in AS

Symptom onset is the key to referring severe AS patients for AVR because of a poor prognosis without AVR. However, it is challenging in some patients who claim to be asymptomatic yet have severe AS. In order to risk-stratify high-risk asymptomatic patients, an exercise test, such as the standard treadmill test, without imaging is reasonable according to recently published guidelines^[16,55-57]. Development of symptoms early on in exercise treadmill testing or an abnormal blood pressure response (below baseline or an inadequate increase of blood pressure < 20 mmHg) are considered indications for surgery in patients with severe AS; however, exercise testing is contraindicated in patients with symptomatic severe AS (Class III)^[16]. Although ESC guidelines^[53] have suggested the use of an increased mean gradient during exercise testing (> 20 mmHg) as an indication for surgery in asymptomatic patients (Class II b), it was not supported in the more recent ACC/AHA guidelines^[16].

Cardiac catheterization

Catheterization has the risk of a small cerebral emboli when the wire crosses the valve^[58]; thus, catheterization is recommended only when there is discrepancy between noninvasive testing, clinical examination, and clinical presentation.

MANAGEMENT

Indications for AVR

It is clear that AVR is recommended in symptomatic

patients with severe AS; however, the decision to recommend early surgery in asymptomatic severe AS patients is still challenging. Indications for AVR in asymptomatic patients are shown in Figure 1, which is based on 2014 AHA/ACC guidelines. Indications for AVR have been consistent between AHA/ACC guidelines and ESC guidelines, though there are slight differences. Asymptomatic patients with severe calcification and a rapid increase in aortic peak transvalvular velocity should be considered for AVR in ESC guidelines with a Class II a indication, but that is a Class II b indication according to AHA/ACC guidelines. Patients with elevated BNP levels, an increase in the Doppler mean pressure gradient with exercise, and excessive LVH may be considered for AVR by ESC guidelines (Class II b), but these are not employed in AHA/ACC guidelines.

Based on the current evidence and guidelines, it is reasonable to consider AVR in severe AS patients when (1) systolic function is decreased (EF < 50%); (2) it is very severe AS ($V_{\max} \geq 5$ m/s, $\Delta P \geq 60$ mmHg); (3) results of the exercise test are abnormal; or (4) there is rapid progression in AS severity ($\Delta V_{\max} > 0.3$ m/s per year) (Figure 1). One must follow patients more closely despite asymptomatic severe AS when there is (1) severe aortic valve calcification; (2) end-stage renal disease; (3) worsening diastolic dysfunction; (4) increased left atrial volume; (5) high brain natriuretic peptide, especially during serial measurements; and (6) new onset of atrial fibrillation or frequent episodes of paroxysmal atrial fibrillation.

Possible beneficial medications

Coronary artery disease and AS have similar risk factors. Additionally, AS has an active inflammation that causes valve calcification. Positive results in experimental and clinical studies on the effectiveness of statins to decrease hemodynamic progression have been published^[59,60], while randomized clinical trials were performed to validate the effect of statins on AS progression^[61]. Although there was the benefit of fewer ischemic cardiovascular events in the treatment groups, no considerable difference in

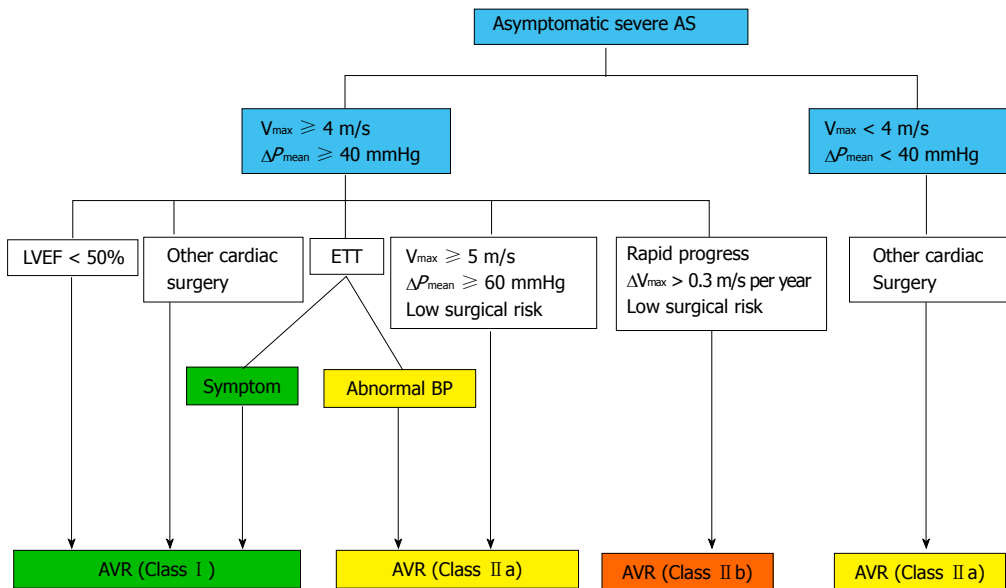


Figure 1 Indications for aortic valve replacement in patients with asymptomatic severe aortic stenosis on the basis of American College of Cardiology/American Heart Association recommendations. Modified from Nishimura *et al*^[16] with permission. ACC/AHA: American College of Cardiology/American Heart Association; AS: Aortic stenosis; AVR: Aortic valve replacement; ETT: Exercise treadmill test; LVEF: Left ventricular ejection fraction.

hemodynamic progression was observed between the treatment and placebo groups^[6]. However, many patients with AS have known concomitant coronary artery disease or risk factors and hyperlipidemia. Guideline-based statin therapy should be considered in these patients regardless of presence of AS.

For AS, the only effective treatment is valve replacement, but it is important to properly manage comorbidities, especially hypertension. Calcific AS is commonly found in the elderly, thus many patients have already been on antihypertensive medication at the time of diagnosis, including diuretics and vasodilators, though diuretics and vasodilators have been thought to be avoided. The current guidelines recommend following guideline-directed medical therapy for hypertension, starting at a low dose and gradually increasing to achieve appropriate blood pressure control. Effectiveness of angiotensin-converting enzyme inhibitors has been investigated on AS in terms of potential benefit on reducing LV fibrosis^[62-64]. Patients with LVOT obstruction caused by discrete upper septal thickening or mid-ventricular obstruction by severely concentric hypertrophy in the setting of AS and hypertension pose a clinical challenge. A β -blocker and appropriate hydration is recommended, and diuretics/vasodilators should be avoided in these patients.

CONCLUSION

Currently, due to an aging population, AS is one of the most common valvular heart diseases. Recent ACC/AHA guidelines provide a new classification system of categorizing valve diseases in patients, including those with AS, that is similar to the classification used in patients with heart failure. In addition, diagnostic strategies and treatment options for the new entity

termed “paradoxical low-gradient severe AS”, despite preserved EF, are given.

Decisions for AVR are based on the presence or absence of symptoms, but proactive investigation with multimodality testing for risk assessment is recommended in patients who are asymptomatic or who have indeterminate symptoms. Exercise stress testing is recommended for asymptomatic severe AS patients in addition to two-dimensional/Doppler echocardiographic testing at rest for risk stratification. If a patient is not physically appropriate for exercise testing, use of a biomarker and multiple imaging modalities, such as CT and MRI with contrast, can complement the risk stratification of asymptomatic severe AS.

Based on the available evidence, it is now reasonable to consider AVR in asymptomatic severe AS patients with (1) decreased EF (< 50%); (2) very severe AS ($V_{\max} > 5$ m/s or $\Delta P \geq 60$ mmHg); (3) an abnormal exercise test; (4) rapid progression of AS ($\Delta V_{\max} > 0.3$ m/s per year); and (5) progressively rising BNP.

Careful attention with frequent follow up is necessary in patients with (1) heavy calcification of the aortic valve (especially end-stage renal disease patients); (2) advanced stage of diastolic dysfunction (\geq stage 2); (3) elevated BNP compared to same age/sex; and (4) new onset of atrial fibrillation.

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