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REVIEW

Multimodality imaging for the diagnosis and assessment of aortic stenosis severity

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ABSTRACT

Introduction: Aortic stenosis (AS) is the most common cause of valvular heart disease. Imaging plays a major role in the diagnosis and evaluation of AS severity.

Areas covered: The present review focuses on new emerging concepts in AS by stressing the substantial value of imaging into the understanding of the complex pathophysiology and management of AS.

Expert commentary: Though, standard 2D echocardiography is often diagnostic multi-modality imaging can be required in patients with doubtful results or to refine the evaluation of AS.

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Aortic stenosis; imaging; cardiac resonance imaging; computed tomography; echocardiography; guidelines; nuclear cardiology

1. Introduction

Aortic valve stenosis (AS) is the most common cause of valvular heart disease in developed countries and increases with age. The prevalence is about 2–4% over 65 years old. Treatment options in patients with AS are mostly driven by the symptomatic status and the severity of AS. Indication of aortic valve replacement (AVR) is recommended by current guidelines when the patient with severe AS develops symptoms (class I) [1]. However, treatment decision is more debated for the management of asymptomatic patients with severe AS and some studies have suggested that an underestimation of symptoms and/or stenosis severity could lead to an inappropriate delayed decision for elective surgery. Echocardiography is the first-line imaging used in AS, but due to some uncertainties about AS severity, a multimodality approach (3D echocardiography, dobutamine or exercise stress echocardiography [DSE, ESE], cardiac multidetector computed tomography [MDCT], cardiac magnetic resonance [CMR], and positron emission tomography [PET-scan]) maybe required to guide therapeutic decision-making. The present review focuses on new emerging concepts in AS by stressing the substantial value of multimodality imaging into the understanding of the complex pathophysiology and management of the disease.

2. The new classification of severe AS

Under the same denomination of severe AS, several entities might be identified that differ in terms of physiopathology, severity of LV remodeling, transvalvular flow rates and pressure gradients, degree of calcifications, consequences, and prognosis. Severe AS is associated with decrease in systolic valve opening, severe aortic valve calcifications, significant LV hypertrophy, impaired myocardial structure and function, and poor outcome in the absence of appropriate treatment. According to guidelines, severe AS is defined on the basis of an aortic valve area (AVA) <1 cm^2, a mean trans-aortic pressure gradient (MPG) ≥40 mmHg, and a peak aortic jet velocity >4 m/s [1–3]. However, discrepancies are frequently observed between these parameters, especially when a low flow (LF) state exists as a result of reduced left ventricular ejection fraction (LVEF) or in case of severe LV concentric remodeling despite preserved LVEF (>50%). Interestingly, normalizing flow in any of these conditions helps distinguishing between severe and pseudo-severe AS [4,5]. Nonetheless, low gradient (LG) can occur despite normal flow (NF) state and can be unexpectedly associated with high gradient (HG) [6]. Severe AS (AVA < 1 cm^2) can thus be subdivided into four flow-gradient patterns in patients with preserved LVEF: NF/LG, NF/HG, LF/HG, and LF/LG [7,8]. LG is defined as a MPG < 40 mmHg. A LF state is commonly defined as an indexed LV stroke volume (SVi) <35 mL/m^2, a cutoff associated with a higher mortality rate and worse outcome in AS [9–11].

The NF/HG pattern is described in 39–72% and is fully coherent with the criteria reached by the guidelines [8,11,12]. The NF/LG pattern is observed in 31–38% of patients and seems to correspond to a less severe degree of AS or to patients exposed to the disease for a shorter period of time [8,12]. The LF/HG pattern is evaluated in 8% of patients with severe AS. Despite apparently preserved LVEF, this group of patients has a reduction of LV output related to intrinsic myocardial dysfunction and significant remodeling [8,13,14]. A LF/LG pattern can also be identified in patients (3–7% in asymptomatic AS; 15–35% in symptomatic AS) with preserved LVEF, namely paradoxical LF/LG AS [7,8,11,13,15–17]. This

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entity seems to have a distinct pathophysiology characterized by severe LV concentric remodeling with smaller LV diastolic cavity size, depressed LV longitudinal systolic function, restrictive LV filling physiology, higher natriuretic peptide levels, lower arterial compliance, and higher arterial and valvular load. The classical LF/LG pattern is observed in patients with poor LV systolic function and is characterized by a decreased LVEF (<50%) and a LG pattern severe AS (AVA < 1 cm^2). It can be observed in up to 10% of patients with AS [3,18,19].

3. Transthoracic Doppler echocardiography: the cornerstone of the evaluation of AS

3.1. Doppler echocardiography

A complete 2D echocardiographic report should contain information regarding valve morphology, give hints regarding etiology of AS, quantify AS severity, and assess upstream consequences (LV and left atrial geometry and function, pulmonary artery pressure, right ventricular function) (Table 1). Complete hemodynamic description of valve stenosis includes systematic reporting of AVA, as assessed by continuity equation, indexed AVA to body surface area (BSA), maximal peak aortic velocity (V_{max}), MPG, and SVi. LV outflow tract diameter (LVOTd) should be measured at the base of the aortic valve cusps or 1–5 mm below the aortic annulus to obtain the largest diameter. However, despite these specific measures, pitfalls in calculating AVA exist. In fact, LVOT is elliptical but current assessment of effective AVA assumes a circular LVOT. This imprecision must always be taken into account for the interpretation of the results. LVOTd should always be reported to allow accurate monitoring of stenosis progression during follow-up. Systematic blood pressure measurement is strongly recommended in order to avoid underestimation of severity (in case of hypertension) and to allow computation of valvuloarterial impedance (Zva), which provides an estimate of the global (valvular + vascular) afterload [20]. Moreover, Zva is an important predictor of LV dysfunction and clinical outcome in severe AS patients. When both blood pressure and Zva (>4.5 mmHg/mL/m^2) are elevated, a repeated examination should be planned after adequate blood pressure lowering therapy. Inaccurate pressure gradient measurements by echocardiography can be suspected in case of small ascending aorta (sinotubular junction diameter <30 mm) due to significant pressure recovery phenomenon (overestimation of transvalvular pressure gradient compared to left heart catheterization in presence of a small ascending aorta) [20,21]. Finally, severe AS is associated with an abnormal LV remodeling pattern, which is assessed by the indexed LV mass and the relative wall thickness.

4. Multimodality imaging assessment of AS severity

Whenever AVA and MPG are in agreement and both indicative of severe AS, 2D echocardiography is usually enough to make an accurate diagnosis. However, in patients with discordant findings, a multimodality imaging evaluation is necessary (Figures 1–4). This multimodality approach may include 2D transoesophageal echocardiography (TOE), 3D transthoracic echocardiography (TTE) and/or 3D TOE, MDCT with the analysis of valve calcium score, stress echocardiography in asymptomatic patients to assess the magnitude of increase in MPG with exercise [22], as well as the presence of exercise-induced pulmonary hypertension [23]. CMR can be used to help in assessing AS severity in patients where echocardiography is suboptimal, but its strength actually resides more in its ability to detect myocardial fibrosis. Recently, PET was reported in patients with AS for the evaluation of valvular calcification and inflammation (Figure 5) [24].

5. Classical AS

TOE can be useful in patients with poor transthoracic acoustic windows and allows measurement of AS severity by planimetry (anatomic AVA). A more accurate measurement of LVOTd is an advantage linked to the higher spatial resolution of TOE. Usually, the quantification of the AVA by the continuity equation is also feasible but requires a correct alignment with flow direction from the transgastric view.

3D echocardiography helps in evaluating AS severity. 3D TTE has the disadvantage of being dependent on transthoracic acoustic window and of having a lower spatial resolution than 3D TOE. 3D echocardiography is often indicated to complement non-conclusive 2D echo. AS severity can be evaluated as follow: (1) guided planimetry of the anatomic AVA using the biplane method, (2) offline planimetry of the AVA using a 3D data set that is cropped to allow direct planimetry at the leaflet tips, (3) optimized computation of effective orifice area (EOA) using the continuity equation and the planimetry of the cross-sectional area of the LVOT without any geometrical assumption from a 3D data set (accurate assessment of stroke volume (SV), especially in case of elliptical LV outflow tract shape for which only the sagittal diameter [often smaller than the coronal one] is measurable by using the parasternal

Table 1. Echocardiographic parameters to report in aortic stenosis.

Etiology and morphology	Grading severity	LV geometry and function	LA and pulmonary pressure
Calcific/Rheumatic/ Congenital/Post-radiotheraphy/Others Tricuspid/Bicuspid/Unknown Mildly/Moderately/Severely calcified	Anatomic AVA: 2D planimetry Effective AVA: *Assessed by the continuity equation* SVi: *To be systematically reported* Aortic peak velocity and mean transaortic pressure gradient: *report the window with the maximal velocity*	LV mass index Relative wall thickness Pattern of LV remodeling: *Normal LV/LV concentric remodeling/LV concentric hypertrophy/LV eccentric hypertrophy* LV ejection fraction Global longitudinal function Mitral E/A and Mitral E/e': *diastolic function grade/pattern; increased LV filling pressure*	Left atrial volume index: *use biplane Simpson's method* Transtricuspid pressure gradient and inferior vena cava diameter and respiratory changes: *to detect pulmonary hypertension*

AVA: Aortic valve area; LV: left ventricular; SVi: indexed LV stroke volume.

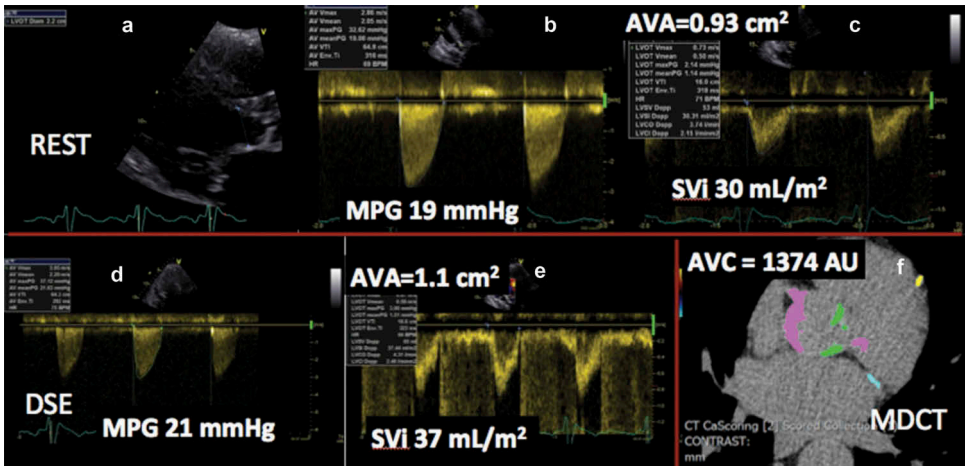

Figure 1. Dobutamine stress echocardiography (DSE) in a male patient with low flow low gradient AS and reduced left ventricular ejection fraction (LVEF = 28%). At rest, the severity of AS was unknown, (aortic valve area (AVA) = 0.9 cm^2, mean pressure gradient (MPG) < 40 mmHg) (Panel a, b, c and d). With dobutamine stress echocardiography (DSE), there was a significant increase in flow reserve (change in stroke volume index (SVi) of 23%) (Panel e); MPG remained <40 mmHg, and AVA reached 1.1 cm^2 suggesting a pseudo-severe AS (Panel e and f). A MDCT indicated an AVC score of 1374 AU, which confirmed that the stenosis was not severe (Panel f) .

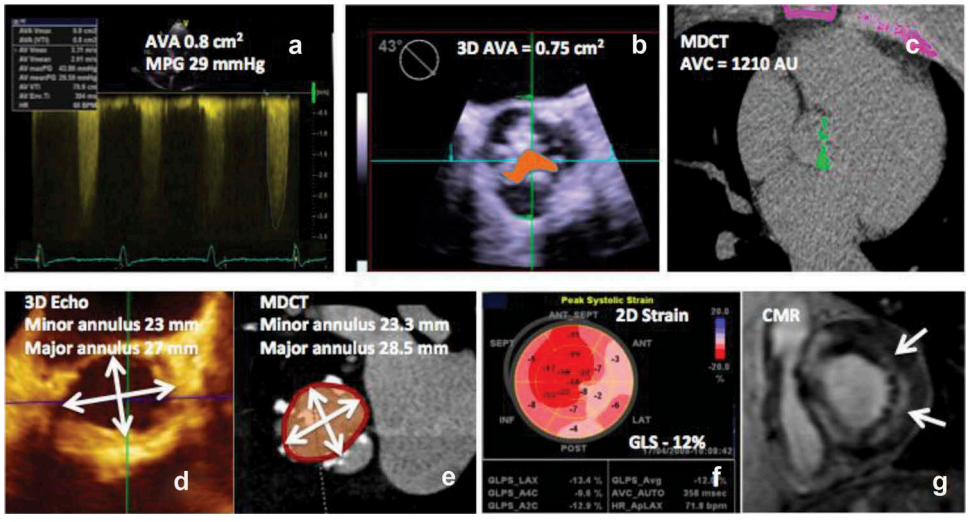

Figure 2. An asymptomatic female patient with low gradient severe AS (aortic valve area (AVA) 0.8 cm^2) (Panel a), high aortic valve calcium score (AVC) (Panel c) (>1200 AU), decreased 2D echo global longitudinal strain (GLS) (Panel f), extensive mid-wall fibrosis at CMR (Panel g). Panel b confirmed severe anatomic aortic stenosis using 3D echo planimetry of the AVA. Elliptical left ventricular outflow tract confirmed by 3D echo and MDCT (Panels de). MPG: mean pressure gradient.

long-axis view), (4) estimation of the 3D derived SV in the continuity equation using full volume acquisition focused on the LV. Of note, anatomic AVA is always greater than effective AVA due to flow constraint distal to the anatomical stenosis. The hemodynamic burden related to AS is more closely related to effective AVA than anatomic AVA [25]. Therefore, they are not interchangeable. Finally, the aortic annulus size (minimum and maximum diameter, annulus perimeter) and shape before transcatheter aortic valve implantation are also more accurately evaluated by 3D TOE [26]. Results are similar to MDCT or CMR-derived diameters and lower the risk of paravalvular regurgitation after transcatheter AVR (TAVR) when compared to 2D TTE [26].

There are two main *stress echocardiography modalities* that can be used to assess patients with AS: (1) DSE is usually reserved for patients with LF/LG AS with depressed LVEF and (2) ESE, which combines an exercise ECG test, performed on a dedicated tilting table equipped with a cyclo-ergometer, and a Doppler TTE allowing continuous imaging monitoring during test. Protocols, guide referral, procedure, and reporting for valve stress echocardiography have been recently discussed by our group [27]. Distinguishing between true severe and pseudo-severe AS and identifying patients at high risk of cardiovascular events are the main indications for valve stress echocardiography in AS. In asymptomatic severe AS, exercise is the optimal stressor and is a class IIa indication in the American Heart Association/American College of Cardiology (AHA/ACC) guidelines while it is strongly advocated in the European Society Cardiology (ESC) recommendations [1,3]. Its low positive predictive value in elderly patients (>70 years old) makes the test poorly interpretable in this age category [28]. Although, a negative exercise test is a reassuring finding in younger patients, the predictive value of the test is improved when combined with echocardiography monitoring of LV function [29], transvalvular pressure gradients [30,31], and pulmonary arterial pressure [23].

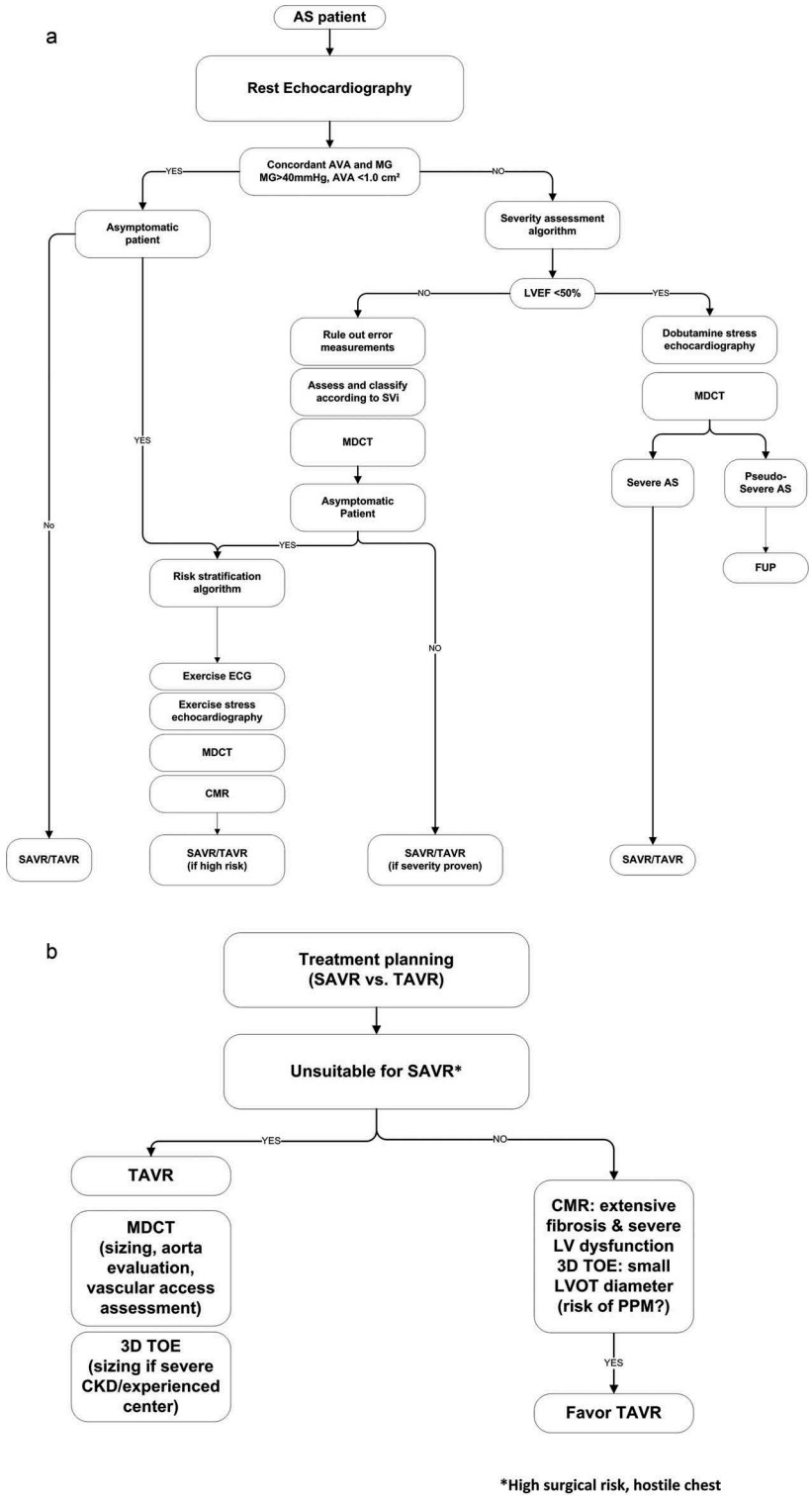

Figure 3. Multi-modality assessment of patients with severe aortic stenosis. Risk stratification and severity assessment (3a). Role of multi-modality imaging in treatment planning (3b). AS: aortic stenosis, AVA: aortic valve area as assessed by the continuity equation, MG: mean transvalvular pressure gradient, SAVR: surgical aortic valve replacement, TAVR: transaortic valve replacement, MDCT: multidetector computed tomography, CMR: cardiac magnetic resonance, FUP: follow-up, SVi: stroke volume index, LV: left ventricle, LVOT: left ventricular outflow tract, 3D TOE: 3 dimensional transoesophageal echocardiography, CKD: chronic kidney disease, PPM: patient prosthesis mismatch.

MDCT is a 3D technique that allows visualization of the aortic valve throughout the cardiac cycle (i.e. visualization of a bicuspid valve) and gives information about LV, coronary anatomy, coronary ostia localization, leaflet length, and aortic root morphology. This technique is especially useful in patients with contraindication to TOE and poor transthoracic acoustic windows. An accurate measurement of AVA is available by planimetry after using 3-multiplanar reformations, from left sagittal oblique and left coronal oblique views generating a cross-sectional view of the aortic valve. Values are

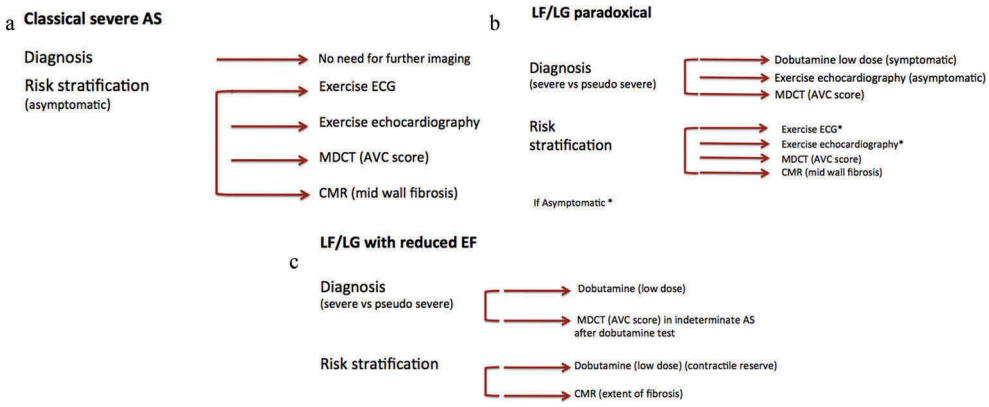

Figure 4. (abc). Role of imaging in the diagnosis and risk stratification of patients with AS according to AS classification.

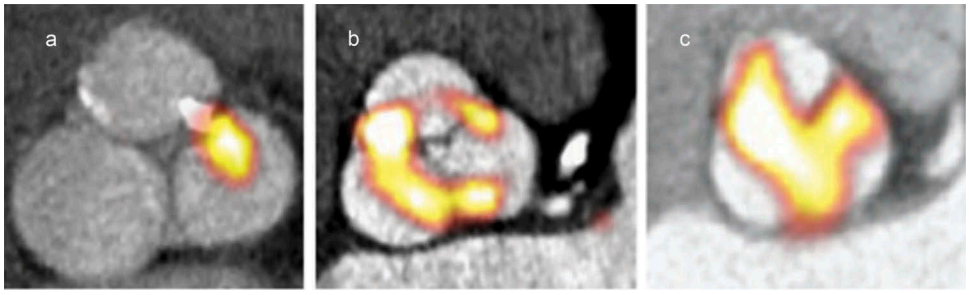

Figure 5. 18 F-Fluoride PET image fused with the CT scans demonstrating increasing severity of abnormal uptake (From panel a to c), indicating regions of calcification activity. Courtesy of Drs. Tania Pawade and Marc Dweck.

slightly superior to TTE AVA and remain flow dependent [32]. The annulus diameters (sagittal/coronal and mean values), area, and perimeter are valuable MDCT sizing parameters of aortic annulus [33]. Typically, the annular size is larger with MDCT, 3D echocardiography, or CMR than when measured with either 2D TTE or TOE (absolute difference up to 1.52 ± 1.1 mm) [32,33]. MDCT is crucial for planning TAVR in order to reduce paravalvular regurgitation, a peculiar problem of the procedure. The main predictors of post-procedural paravalvular regurgitation are well known: protruding annular calcium into the lumen (>4 mm), severe aortic annular calcification, and undersizing of annulus size [34,35]. Furthermore, MDCT is used to evaluate the aorta and peripheral vasculature that is important in TAVR prosthesis choice and vascular access route. Aortic valve calcium score can also help discriminate severe from non-severe AS in patients with discordant echocardiography results. Different cutoff values for severe AS in men (≥2000 Agatston units (AU) or ≥480 AU/cm^2) versus women (≥1200 AU or ≥290 AU/cm^2) have been proposed [36,37].

CMR, a noninvasive technique without ionizing radiation, has showed to be useful to assess both anatomic AVA and effective AVA. However, the role of this technique to measure AVA is marginal and is not yet related to AS diagnosis and prognosis. This modality is used to quantify AS severity in patients with difficult transthoracic acoustic windows and contraindication for TOE [38]. CMR planimetry is however a less than optimal approach in patients with calcific AS, especially when a nonplanar orifice exists [39]. Other standard measures of stenosis severity can be obtained with CMR: peak anterograde velocity, pressure gradient, and effective AVA. CMR could also be used to assess LVOT area and accurate assessment of SV (caveat is the absence of significant mitral regurgitation). It may be useful in patient with suspected LF/LG severe AS to confirm valve area and flow states [38]. Velocities are often slightly underestimated with CMR when compared with Doppler echocardiography [40]. Like MDCT, CMR mostly allows measurement of anatomic AVA, which is not equivalent to the effective AVA calculated from the continuity equation. Rarely, in the pre-procedural work-up for patients' selection for TAVR, CMR can also be used to evaluate prosthesis size and vascular route. CMR also has the ability to characterize the pattern and volume of myocardial fibrosis (focal/diffuse and subendocardial/mid-wall) [41,42]. CMR late gadolinium enhancement provides information on replacement focal fibrosis [41] while T1-mapping extrapolates reactive interstitial fibrosis from measurement of extracellular volume [43]. CMR may also quantify lipid, fibrous, and calcium components within the aortic valve cusps [44].

PET/CT has emerged as a new modality to complete the evaluation of patients with AS. PET and CT combine functional and anatomical information. The degree of calcification and inflammation within the aortic valve leaflets may be used to assess disease activity in AS [24]. ^{18}F-sodium fluoride (^{18}F-NaF), a tracer identifying calcium deposits in human atherosclerotic vascular tissue, could be useful for measuring the calcification activity in AS [24]. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is another PET tracer whose uptake has been linked to macrophage burden

in the carotid arteries and which can be used to measure metabolic activity in the aortic valve as a surrogate for inflammation [24,45].

Calcific aortic valve disease (CAVD) encompasses the range of disease from initial alteration in the cell biology of the leaflets to end-stage calcification resulting in LVOT obstruction. As mentioned previously by a review of the National Heart and Lung and Blood Institute Aortic Stenosis Working Group, it will be crucial to understand the basic valve biology (e.g. early events, mechanisms, and regulatory effects) of CAVD, including signaling pathways and the roles of valve interstitial and endothelial cells and the autocrine and paracrine signaling between them, the extracellular matrix and matrix stiffness, the role of age-related changes in both valve cells and extracellular matrix, the interacting mechanisms of cardiovascular calcification and physiological bone mineralization, and microscale mechanotransduction and macroscale hemodynamics [46].

6. LF/LG AS with reduced LVEF

A poor LV systolic function may lead to a significant decrease in LV SV and to consequently lower gradients due to the dependency of gradients on flow, making the issue of discordance between AVA and MPG less unexpected in patients with reduced LVEF. The role of *DSE* to normalize flow and distinguish between severe and pseudo-severe AS is well established in this setting [3].

Dobutamine (up to 20 µg/kg/min) [4] as a stressor is recommended (class IIa) in these patients [3]. A true severe AS (LV systolic dysfunction as a result of AS) is identified when the increase in SV (>20%) is accompanied by a rise in MPG (≥40 mmHg) but not in AVA (change < 0.3 $cm^{2;}$ AVA ≤ 1.0–1.2 cm^2) under dobutamine infusion [1]. When the AVA increases (change > 0.3 cm^2; AVA > 1.2 cm^2) but the MPG remains <40 mmHg, a pseudo-severe AS (LV systolic dysfunction not related to AS) is present [1]. When the SV increase is less than 20% and no significant changes in MPG and AVA are observed, AS severity remains indeterminate. However, ambiguous flow responses during dobutamine administration may lead to erroneous interpretation of the test. Computing AVA (i.e. projected AVA) at a standard flow rate of 250 mL/s can overcome the limitation of the test [47,48]. A projected AVA >1.0 cm^2 or indexed projected AVA > 0.55 cm^2/m^2 underlined the presence of pseudo-severe AS [47]. When a doubt persists about the severity of AS, other imaging tools are often used (i.e. MDCT) [36]. Aortic valve calcium score by MDCT is particularly useful for patients with discordant findings on echocardiography or in patients in which DSE is not feasible or provides inconclusive results [36]. High calcium score is in favor of severe AS.

7. LF/LG AS with preserved LVEF

In this category, confirmation of AS severity often requires multimodality imaging approaches. After ruling out measurement errors, checking for small AVA related to small BSA, eliminating causal factors of LF–LG AS (pronounced concentric LV remodeling, small LV cavity, reduced longitudinal function, moderate-to-severe LV diastolic dysfunction, mitral stenosis, mitral regurgitation, tricuspid regurgitation, atrial fibrillation), and under strict control of the systolic blood pressure, a diagnosis of LF/LG AS can be suspected. Confirmation of the LF state is then warranted by 2D/3D echo volumetric methods or CMR and differentiation between true versus pseudo-severe stenosis can be done using stress echocardiography if feasible or MDCT (high AVC).

8. Risk stratification

Prognostication in AS involves a complex interplay between disease severity, LV function, and vascular load (Table 2).

At *echocardiography*, >moderate aortic valve calcification [49], a high aortic peak velocity (>4 m/s and even more if >5 m/s) [49–51], an enlarged left atrial size (indexed area >12.4 cm^2/m^2 [52], an inappropriately high LV mass (>110% of that expected for body size, gender, and wall stress) [53], a reduced mitral annulus systolic and late diastolic velocity (s'< 4.5 cm/s, a' < 9 cm/s) [52], a decreased global

Table 2. Imaging risk findings in aortic stenosis.

Imaging parameters	Cutoff values
Asymptomatic aortic stenosis with preserved left ventricular ejection fraction	
Peak aortic velocity	>4 m/s
Indexed left atrial size area	>12.4 cm^2/m^2
High left ventricular mass	>110% of that expected for body size, gender, and wall stress
Reduced mitral annulus systolic velocity	s' < 4.5 cm/s
Late diastolic velocity	a' < 9 cm/s
Decreased global longitudinal strain	≤−15.9%
Exercise increase in mean pressure gradient	>18–20 mmHg
Exercise fall in systolic blood pressure	>20 mmHg
Absence of contractile reserve	<5% exercise increase in left ventricular ejection fraction
Exercise pulmonary hypertension	>60 mmHg
Rapid rate of aortic stenosis progression	≥0.3 m/s/year
High global afterload	Zva > 4.5 mmHg/mL/m^2
Severe aortic valve calcification at MDCT	≥1200 AU in women or ≥2000 AU in men
Fibrosis at CMR	Mid-wall pattern
Marker of calcification activity by PET–CT	Increased ^{18}F-NaF uptake
Aortic stenosis with reduced left ventricular ejection fraction	
Aortic valve calcification	Severe
Aortic mean pressure gradient	<20 mmHg
Absence of flow reserve	<20% increase in stroke volume during dobutamine test
LV function	Severely impaired
Myocardial fibrosis	Severe and diffuse

longitudinal strain (≤−15.9%) [54], an exercise increase in MPG ≥ 18–20 mmHg [30,31], the absence of flow reserve (less than 20% increase in SV during dobutamine infusion) [55], the absence of contractile reserve (no or <5% exercise increase in LVEF) [22], an exercise pulmonary hypertension (>60 mmHg) [23], or a rapid rate of AS progression (≥0.3 m/s/year) [49] are all strong predictors of cardiac events in AS. A high global afterload (Zva > 4.5 mmHg/mL/m^2, the ratio between the sum of systolic arterial pressure and MPG, and the SVi) is associated with an increased risk of LV dysfunction and a reduced event-free survival [54].

At MDCT, severe aortic valve calcification (≥1200 AU in women and ≥2000 AU in men) independently predicts excess mortality in AS. Individualized risk stratification can also be performed in asymptomatic patients with severe AS by assessment of the aortic calcium load [56].

At CMR, up to 38% of patients with moderate or severe AS may exhibit a mid-wall pattern of myocardial fibrosis [41]. AS is a common disease in which failure of the aortic valve to completely open imposes an abnormally high-pressure load upon the LV. Irrespective of the etiology causing AS, the ensuing pressure overload results in the manifestation of two distinct but overlapping processes. The first process is characterized by concentric LVH. The second process occurs within the myocardial extracellular matrix and leads to progressive myocardial fibrosis, reduced ventricular compliance, and impairment in diastolic filling, i.e. diastolic dysfunction. It is this second phase of progressive LV myocardial fibrosis that contributes to the progression of LV diastolic dysfunction, and eventually to the signs and symptoms of heart failure. Mid-wall fibrosis is an independent predictor of mortality in patients with moderate and severe AS. It has an incremental prognostic value over ejection fraction and may provide a useful method of risk stratification. By histopathology, hearts with severe AS present with both interstitial diffuse reactive fibrosis as well as focal replacement fibrosis. Diffuse fibrosis appears to result from alterations in the balance of matrix metalloproteinases and their specific tissue inhibitors subsequent to the overstimulation of the angiotensin–renin system. Replacement fibrosis involves myocyte death by apoptosis or necrosis. Replacement fibrosis is associated with worse prognosis and higher postoperative mortality [41,42]. Although correlated with symptomatic status, diffuse myocardial fibrosis has not yet been validated as an outcome finding [57].

At PET/CT, ^{18}F-NaF, as a marker of calcification activity, is a good predictor of aortic valve calcium score progression by MDCT at 1 year [58]. Additional studies are needed to evaluate the prognosis role of ^{18}F-NaF PET/CT in AS.

9. Timing of intervention and follow-up

Timely intervention depends upon true estimates of disease severity, symptomatic status, and the degree of LV dysfunction [1,3]. Standard of care, once severe AS becomes symptomatic at rest or on exertion (angina, syncope, dyspnea) and/or LVEF falls below 50%, is surgical AVR (SAVR) or TAVR in patients not suitable for surgery (class I indication) [1,3]. Another accepted class I indication for AVR in asymptomatic severe AS is the need for cardiac surgery for any other reason such as coronary bypass grafting or surgery of the ascending aorta [1,3]. The management of asymptomatic patients remains controversial and is based on individual risk stratification. No randomized trials have shown beneficial effects of lipid-lowering drugs on disease progression [59–61]. Moreover, there is a lack of randomized controlled trials investigating the effect of AVR in earlier stages of AS. Prophylactic AVR is thus not recommended. However, the 'wait for symptoms' strategy requires a careful follow-up – which is not necessarily applicable to all patients – with a prompt identification of the onset of symptoms. Indeed, lack of symptoms recognition portends a high risk of death [62]. The risk of death also increases with symptom severity and if the waiting period for surgery in newly symptomatic patients is too prolonged. Additionally, there is a risk of shifting from a low- to a high-risk category due to changes in comorbidities (i.e. evolution of lung disease). Ideally, the surgical decision should be made sufficiently late to outweigh the risk of operation and early enough to avoid irreversible damage of the LV myocardium.

9.1. Asymptomatic severe AS

Up to 50% of patients with severe AS are asymptomatic [63]. Management of these patients requires careful risk benefit analysis promoting a tailored approach to treatment. After confirmation of AS severity, determination of whether the patient is truly asymptomatic on exercise ECG (treadmill or upright bicycle) is pivotal. In the absence of exercise-induced symptoms, the presence of a very severe AS (maximum aortic velocity ≥5.0–5.5 m/s) and/or an exercise fall >20 mmHg in systolic blood pressure is accepted indications for AVR (class IIa) [1]. The presence of factors of rapid AS progression (older age, severe aortic valve calcification, known coronary artery disease), of concomitant adverse prognostic factors (high brain natriuretic peptide (BNP) level, high Zva, enlarged left atrial, decreased 2D speckle tracking longitudinal function, etc.), of comorbidities (i.e. chronic obstructive pulmonary disease), or in case of inconclusive exercise testing (<20 mmHg increase in systolic blood pressure, >3–5 mm ST segment depression, >70 years old patient) makes reasonable suggesting further imaging risk assessment or closer follow-up (every 3 months). The incremental value of ESE has been shown in various studies [30,31]. An increase in MPG >20 mmHg during test represents a class IIb indication for AVR in low surgical risk patients (ESC guidelines) [1]. The presence of pulmonary hypertension and/or a limited contractile reserve at ESE is additional risk markers of poor prognosis [22,23]. When present, they should also favor closer follow-up. Coronary angiography should be performed in case of inducible ischemia though it may result from limited coronary reserve without significant epicardial stenosis. Other imaging tools such as calcium score assessment by MDCT or evaluation of myocardial fibrosis by CMR are not yet routinely indicated for risk stratification. When a rapid progression of AS (≥0.3 m/s/year) coexists with >moderate aortic valve calcification, AVR is a class IIa indication (ESC) [1]. When at low risk, patients should be followed-up as recommended and educated to self-report onset of new symptoms to physician immediately.

9.2. LF/LG AS with reduced LVEF

In this AS category, the survival rate is usually low (<50% at 3-year follow-up) under conservative treatment, but the operative mortality is high (6% to 33%) if treated surgically [55,64]. Factors of poor prognosis include comorbidities (diabetes, coronary artery disease, multivessel disease, atrial fibrillation), very low MPG (<20 mmHg) as an estimate of profound intrinsic myocardial contractility impairment, extensive myocardial scar/fibrosis, high BNP level (>550 pg/mL), and the absence of flow reserve (<20% increase in SV) at dobutamine test [16,55,65]. So, the main challenge in this AS group is to identify patients who may benefit from AVR.

These patients are typically symptomatic and the echocardiographic examination reveals a dilated LV with markedly decreased LVEF. The aortic valve often looks like severely calcified and distinction with moderate AS requires the use of additional imaging tests. DSE is classically used to identify residual flow reserve, which serves to distinguish severe from pseudo-severe AS and for risk stratification.

Pseudo-severe AS accounts for 30–40% of patients with LF/LG AS and reduced LVEF [47,66,67]. The outcome of these patients is comparable to non-valvular heart failure patients [67]. Therefore, they require optimal heart failure medical treatment and careful follow-up to ensure that AS has not become severe. AVR might become an option if severely limiting symptoms persist.

LV flow reserve by DSE carries very strong estimate of operative risk (mortality up to 10% with flow reserve vs. 30% without flow reserve) [18,55,68] but does not permit prediction of LVEF recovery, improvement in symptomatic status, and late survival after AVR [69]. Therefore, AVR should not be denied on the sole absence of LV flow reserve. When ambiguous DSE results are obtained (insufficient increase in SV, even for calculation of projected EOA), quantification of valve calcification by MDCT may also be useful. A score >1650 AU provides good accuracy to distinguish true severe from pseudo-severe AS [70].

Both AHA/ACC and ESC guidelines support AVR (class IIa) in patients with LF/LG severe AS and reduced LVEF when LV flow reserve is present. Coronary artery bypass graft surgery should also be contemplated at the time of AVR, whenever necessary. AVR can certainly be considered (class IIb) in patients with no LV flow reserve when either a low projected EOA (<1.2 cm^2) or a high calcium score is noted. In addition, the absence of extensive myocardial scar/fibrosis on CMR may be another incentive to AVR (higher operative mortality if extensive fibrosis) [16,71]. TAVR could be a valuable alternative to SAVR, particularly when prohibitive risks are underlined. The survival rate after TAVR however remains lower than in patients with preserved LVEF but the recovery of function is better and more rapid than in those undergoing SAVR [72]. The better hemodynamic performance of TAVR and the potential cardiodepressive effects (ischemia/reperfusion, inflammatory response, cardioplegia, oxidative stress, etc.) related to open-chest surgery that contribute to this observation might be counterbalanced in the long run by the higher prevalence of paravalvular regurgitation after TAVR. Of note, ESC guidelines consider LVEF <20% as a relative contraindication for TAVR [1].

9.3. LF/LG AS with preserved LVEF (paradoxical LF LG)

Most of these patients are symptomatic, of female gender, and have concomitant systemic arterial hypertension [11,73]. The echocardiographic findings are suggestive with severely calcified aortic valve, severe LV concentric remodeling (relative wall thickness >0.5), small LV cavity (end-diastolic volume index <55 mL/m^2), reduced SV (<35 mL/m^2), decreased 2D speckle tracking longitudinal function (global strain <16%), and restrictive LV diastolic pattern in the context of <40 mmHg aortic MPG and <1 cm^2 EOA [74]. Misdiagnosing this AS category may lead to an inappropriate timing of follow-up with an unnecessary delay of AVR.

Cardiology confirmation of AS severity often requires multimodality/imaging approaches. Differential diagnosis can be made by challenging measurements of SV and AVA with those obtained by other independent methods (volumetric methods using echocardiography or CMR) and by assessing other typical features associated with paradoxical LF/LG AS such as increased Zva, severe aortic valve calcification by MDCT, or patchy myocardial fibrosis at CMR. When doubt still persists, evaluation LV flow reserve and calculating projected AVA could be of help as in patients with reduced LVEF.

Paradoxical LF/LG AS conveys a poor outcome regardless of the symptomatic status [8,75,76]. Though the benefit of AVR is not yet totally proven, these patients clearly have a worse prognosis if treated medically [76–78]. Therefore, AVR is a class IIa indication in symptomatic patients with LF/LG and confirmed fixed severe AS. In these patients, the choice of SAVR versus TAVR depends on the individual risk. TAVR is an attractive alternative as it is less invasive (less risk of further myocardial impairment due to surgical conditions) and carries a lower risk of prosthesis–patient mismatch. Whether TAVR brings better survival than SAVR remains to be addressed. In practice, TAVR might become a first choice in elderly patients with small aortic annuli and aortic root sizes [11]. In younger patients, SAVR is the recommended therapeutic option.

10. Conclusion

AS is the most common valvular heart disease encountered in clinical practice in the western world. Severity assessment relies in most of the cases on resting echocardiography. However, a multimodality imaging approach including stress echocardiography, MDCT, CMR, and/or PET/CT maybe needed in 25–30% of cases with discordant resting echocardiography findings. Moreover, each of these techniques has proven useful in risk stratification of patients with severe AS. Nowadays, the clinicians should be more and more familiar with these techniques, with their advantages, and also with their limitations, to implement them when needed in order to improve individual patient outcome.

11. Expert commentary

Although, AS is the most frequent valvular disease, much remains to be done for its accurate assessment. Echocardiography remains the cornerstone in the evaluation of AS. In most cases, it provides the diagnosis, allows the

assessment of disease severity, and permits stratification of the individual risk. Several additional echocardiographic modalities (3D echocardiography, stress echocardiography) can be used to refine the conventional echo features of AS degree. 2D speckle tracking of myocardial deformation has gained interest in the routine clinical arena and can be part of the echo report in AS. A decrease in global longitudinal strain seems to be a robust marker of poor prognosis. 3D echocardiography is used to evaluate LV volumes and function, and confirm Doppler-derived SV value. Stress echocardiography provides incremental prognostic information over resting echocardiography or exercise testing parameters in asymptomatic AS. In patients with LV systolic dysfunction, DSE is useful to distinguish severe AS from pseudo-severe AS and predict perioperative mortality. MDCT is useful to evaluate aortic valve calcium load, which is a marker of AS severity and poor outcome. MDCT is currently valuable in patients with LF/LG AS and decreased LVEF or paradoxical AS. Detection of myocardial fibrosis by CMR might be of interest to identify the extent of myocardial abnormalities and their potential reversibility after treatment. PET imaging might be of interest to detect high aortic valve metabolic activity.

12. Five-year view

Imaging will continue to keep a major role in the assessment, monitoring, and treatment guidance of patients with AS. 3D echocardiography will likely be used routinely in heart valve expert centers. Analysis of global longitudinal function will be largely implemented in the echo lab, and probably 3D myocardial deformation will be validated in AS. Prospective studies will be performed to assess the clinical usefulness of diffuse LV myocardial fibrosis on CMR T1-mapping. A risk score comprising several resting and stress echocardiographic parameters, various biochemical markers (such as N-terminal pro BNP and BNP), the degree of LV myocardial fibrosis and the calcium burden (MDCT) could be prospectively tried out in asymptomatic AS patients. To date, existing risk scores have not been validated in large cohort of patients [12,79]. Whether symptomatic patients with moderate AS may benefit from AVR or what is the impact of TAVI in LF/LG AS (moderate or severe) without flow reserve is unknown. The use of a stepwise imaging approach might identify potential responders to these treatments. PET/CT imaging of inflammation and calcification activity may revolutionize patient care with AS at earlier disease stage (mild-to-moderate AS), by assessing the effects of targeted medical treatment on AS progression. Accordingly, in the future, probably a multi-marker (clinical characteristics, and imaging and biochemical features) risk stratification approach may be needed in patients with AS.

Key issues

- AS is the most common cause of valvular disease in developed countries.
- Decision to treat is taken only in patients with severe AS who develop symptoms or have a LVEF lower than 50%. In asymptomatic patients with severe AS, decision to treat is based on individual risk stratification, but many controversies still exist.
- Echocardiography is still the first line imaging modality to assess severity and stratify risk in patients with AS. However, due to some discrepancies between the echocardiographic parameters that define severity, a multi-modality imaging approach may be required to define severity and guide therapeutic decision-making.
- This multimodality approach may include 2D/3D TTE, or 2D/3D TOE, MDCT with the analysis of aortic valve calcium score, stress echocardiography, CMR, and more recently PET imaging.
- Recently, a new echocardiography based classification, taking into account flow-gradient patterns, has been described in patients with AS and preserved LVEF, aiming to reconcile discrepancies sometimes found during TTE examination. Consequently, AS can be subdivided into 4 flow-gradient patterns: NF/LG, NF/HG, LF/HG and LF/LG AS.
- In patients with LF/LG AS and reduced LVEF, DSE is used to normalize flow and distinguish between severe and pseudosevere AS. Patients with flow reserve and 'true severe' AS can benefit from SAVR or TAVR, if considered at high surgical risk. Patients without flow reserve, have high perioperative mortality, but may benefit from TAVR/SAVR, if severity is proved by a flow-independent method, such as MDCT. However, in this particular case, SAVR has high perioperative mortality.
- At echocardiography, a high aortic peak velocity, an enlarged left atrium, a high LV mass, a reduced mitral annulus systolic and diastolic velocity, a decreased global longitudinal strain, a significant exercise-increase in MPG, the absence of flow or contractile reserve, an exercise pulmonary hypertension and a rapid rate of AS progression are strong predictors of cardiac events in AS.
- At MDCT, severe aortic calcification independently predicts excess mortality in AS.
- At CMR replacement and diffuse myocardial fibrosis can be detected and seems to be associated with a worse outcome.
- 18 F-NaF PET/CT identifies the calcification activity in the aortic valve.
- In case of LF/LG AS with preserved LVEF (paradoxical) confirmation of AS severity often requires multi-modality/imaging approaches. This pattern conveys a poor outcome regardless of the symptomatic status.

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Declaration of interest

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