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ECHOCARDIOGRAPHY (G DWIVEDI, SECTION EDITOR)

Low Gradient Aortic Stenosis: Role of Echocardiography

Ian G. Burwash[1] · David Messika-Zeitoun[1]

Abstract

Purpose of Review The purpose of this paper is to review the current role of echocardiography in the evaluation of patients with low gradient severe aortic stenosis (LG severe AS).

Recent Findings Discordant grading of AS severity, in which a small aortic valve area coexists with a small gradient, can result in diagnostic and therapeutic dilemmas. Transthoracic, transesophageal, and stress echocardiography play pivotal roles in reconciling the discordance and clarifying AS severity. Three physiologic categories of LG severe AS can be identified (classical low flow (LF) LG AS, paradoxical LF-LG AS, and normal flow LG AS), each with different prognostic and therapeutic implications. Echocardiographic measures of the severity of the valve stenosis, left ventricular function (and functional reserve), and right heart disease provide important prognostic information to assist with patient management.

Summary A systematic comprehensive approach using echocardiography is essential in LG severe AS to understand the reason for the discordant hemodynamics, to confirm AS severity, and to guide therapeutic decision-making.

Keywords Aortic stenosis · Low gradient aortic stenosis · Low flow aortic stenosis · Aortic stenosis severity · Aortic valve area · Stress echocardiography · Dobutamine echocardiography

Introduction

Aortic stenosis (AS) is the most common valve disease with an age-related prevalence of approximately 10% in patients more than 75 years of age [1, 2]. While the presence of a systolic murmur is often the first clue that AS is present, echocardiography plays a pivotal role in confirming the diagnosis, grading the severity, evaluating the ventricular response, and in combination with the patient's symptomatic state, determining the necessity for aortic valve replacement (AVR) or the frequency of follow-up during conservative management [3, 4••].

In clinical practice, three hemodynamic parameters should be routinely measured in all AS patients to evaluate the severity: Peak transvalvular velocity (Vmax), mean transvalvular pressure gradient (MG) derived using the Bernoulli equation, and aortic valve area (AVA) derived using the continuity equation [5••]. The assessment of hemodynamic severity is primarily based on Vmax with a velocity ≥ 4 m/s identifying high gradient (HG) severe AS in the absence of a reversible high flow state [3, 4••, 5••]. Since Vmax and MG and are strongly correlated, a MG ≥ 40 mmHg also identifies HG severe AS. These thresholds are typically associated with an AVA ≤ 1.0 cm^2 or an indexed AVA ≤ 0.6 cm^2/m^2. In patients with Vmax < 4 m/s or MG < 40 mmHg, it is essential to calculate AVA to determine AS severity. An AVA > 1.0 cm^2 suggests mild or moderate AS, while an AVA ≤ 1.0 cm^2 raises the possibility of severe AS despite the low Vmax or MG [3, 4••, 5••]. This latter situation has been referred to as "low gradient (LG) severe AS" and is observed in up to 30% of AS patients [6]. When encountered in clinical practice, LG severe AS can lead to confusion as to the actual severity of the valve stenosis and whether AVR should be undertaken if the patient is symptomatic or has left ventricular (LV) dysfunction.

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✉ Ian G. Burwash
iburwash@ottawaheart.ca

David Messika-Zeitoun
DMessika-zeitoun@ottawaheart.ca

[1] Department of Medicine, Division of Cardiology, University of Ottawa Heart Institute, University of Ottawa, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada

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Causes of Low Gradient Severe AS (Fig. 1)

Measurement Error

The calculation of AVA by continuity equation requires the measurement of the LV outflow tract (LVOT) velocity using pulsed Doppler, the transvalvular velocity using continuous-wave Doppler and the cross-sectional area of the LVOT, usually obtained by measuring the LVOT diameter and applying a circular assumption for the diameter–area relationship [5]. Despite the necessity for multiple measurements, AVA calculated by continuity equation shows good agreement with AVA derived invasively by Gorlin equation [7, 8]. However, an error in the acquisition or measurement of any of these variables can lead to an inaccurate AVA, discordant hemodynamic indices, and LG severe AS.

AS Velocity/Mean Pressure Gradient

It is critical to interrogate the aortic valve from multiple acoustic windows, preferably using a dedicated continuous-wave Doppler probe, to identify the highest transvalvular velocity [9]. The right parasternal window is the site of Vmax in up to 50% of AS patients and failure to interrogate the valve from this window can result in the AS severity grade being underestimated in 26% of patients [9, 10]. In addition, ≈ 10% of patients with HG severe AS will be erroneously identified as LG severe AS because of the quadratic relationship between transvalvular velocity and MG, but the linear relationship with AVA [9, 10]. The right parasternal window is more likely to identify Vmax when the LV-aortic root angulation in the parasternal long-axis view is < 115°, and attention to these anatomic features can help guide efforts during the examination [10].

Stroke Volume

LVOT stroke volume (SV) is a frequent source of error if care is not taken during technical acquisition. The transducer should be positioned at the apex, or often laterally on the left ventricle, to align the ultrasound beam down the barrel of the LVOT parallel to flow. The pulsed-Doppler sample volume should be 3–5 mm in size and positioned in the LVOT just proximal to the flow convergence region. The velocity signal should have minimal spectral dispersion, and the modal velocity should be traced [5]. Oblique interrogation of LVOT

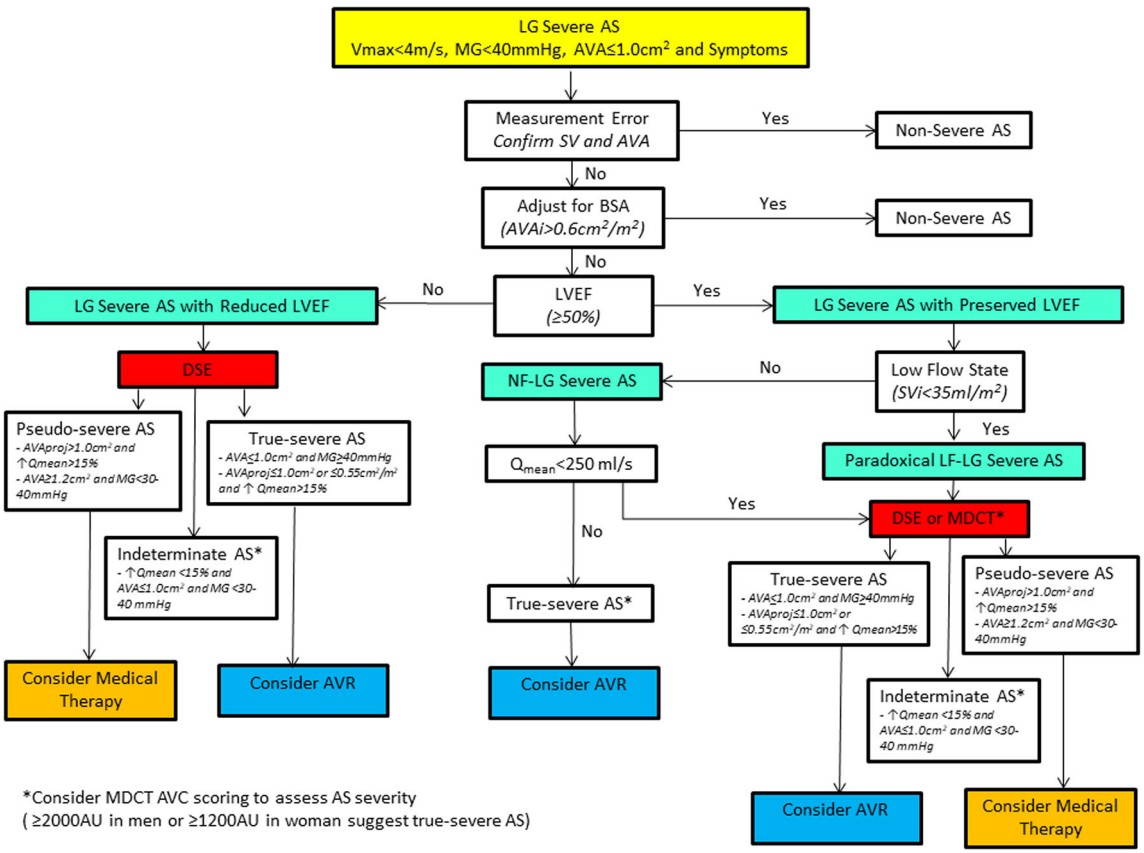

Fig. 1 Suggested algorithm for the investigation and management of patients with LG severe AS. AS = aortic stenosis; AU = Agatston units; AVA = aortic valve area; AVAi = indexed aortic valve area; AVAproj = projected AVA at 250 ml/s; AVC = aortic valve calcium; AVR = aortic valve replacement; DSE = dobutamine stress echocardiography; LG = low gradient; LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography; MG = mean gradient; NF = normal flow; Qmean = mean transvalvular flow rate; SVi = stroke volume index

flow due to medial positioning of the transducer, or excessive apical positioning of the sample volume, will lead to an underestimation of SV, an inaccurate small AVA, and the potential erroneous diagnosis of LG severe AS.

The LVOT diameter can be challenging to measure and controversy exists as to the precise location to make the measurement [5, 11]. Guidelines suggest that the LVOT be measured in mid-systole at the site at which the LVOT velocity is acquired, often 5–10 mm apical to the valve. However, the LVOT geometry is variable with rectangular-, funnel-, and hourglass-shaped morphologies and markedly different areas will be calculated depending on the site of the diameter measurement. We believe the LVOT diameter should be measured at the site of cusp insertion into the aortic annulus. Continuity equation and Gorlin equation AVA shows the best agreement when the LVOT diameter is measured at the aortic annulus, rather than 5 or 10 mm proximal to the annulus [12]. The measurement should be made from the base of the right coronary cusp to the left and non-coronary cusp interleaflet commissure to avoid underestimating the LVOT diameter.

Multi-detector computed tomography (MDCT) and 3D-echocardiography have shown that the LVOT is elliptically shaped rather than circularly shaped in many AS patients [13–16]. The LVOT diameter measured in the parasternal long-axis view correlates more with the minor axis dimension of the ellipse, and use of a circular assumption can potentially lead to a 26% underestimation of SV and AVA [14]. Some investigators have suggested using fusion imaging to measure SV and AVA, in which LVOT area is measured by MDCT and Doppler data is acquired by transthoracic echocardiography, and report reclassifying one-third of LG severe AS patients as concordant moderate AS [16]. However, this approach also leads to a decrease in the prevalence of concomitant concordant moderate AS and increases the prevalence of discordant HG moderate AS [17]. Clinically, the prediction of adverse events in AS patients is not improved by using fusion imaging compared with the standard continuity equation, but rather only increases the AVA threshold for excess mortality from 1.0 cm^2 using the standard continuity equation to 1.2 cm^2 using fusion imaging [18]. As the LVOT is more elliptically shaped in systole the farther down from the more circularly shaped aortic annulus, using an annular plane site for calculating LVOT area helps limit the error to a 10% underestimation of SV and AVA [19, 20].

Identifying Measurement Error as the Potential Causes of Low Gradient Severe AS

Measurement error should always be the first consideration when presented with LG severe AS. Aortic leaflet morphology and mobility should be visually evaluated for consistency with the quantitative measures, and the quality of the Doppler and 2D images should be critically reviewed. LVOT SV is the frequent source of error, and the measurement should be corroborated using another complementary echocardiography technique such as the Teichholz method, modified Teichholz method, biplane method of disks, or preferable 3D-echocardiography, considering inherent limitations of each technique [21–23]. LVOT diameter at the annulus correlates with the patient's body surface area (BSA) and can be predicted by the formula [24]:

$$\mathrm{LVOTdiam} = (5.7 \times \mathrm{BSA}) + 12.1$$

In 90% of patients, the LVOT diameter is within 2 mm of predicted by this formula. An LVOT diameter below this threshold should raise suspicion that the diameter has been underestimated. There is a caveat for bicuspid aortic valves and obese patients, where the formula may underestimate or overestimate the LVOT diameter, respectively.

The velocity ratio (VR), a ratio of transvalvular and LVOT velocity-time integrals, provides a measure of AS severity independent of LVOT area [5]. A VR < 0.25 suggests severe AS, while a VR > 0.25 suggests non-severe AS. In the presence of LG severe AS, a VR > 0.25 should raise suspicion that the LVOT diameter may be underestimated.

An attempt should also be made to corroborate the continuity equation AVA with planimetry by 2D or 3D-transthoracic or transesophageal echocardiography [14, 25]. An AVA ≤ 1.0 cm^2 on planimetry confirms severe AS. An AVA slightly greater than 1.0 cm^2 does not exclude severe AS since the effective orifice area is usually slightly smaller than the anatomic AVA.

Impact of Body Size

Since cardiac output correlates with body size, the physiologic significance of a valve narrowing depends on the patient's body size. In a small individual, AVA ≤ 1.0 cm^2 may not represent severe AS and Vmax and MG may be < 4 m/s and < 40 mmHg, respectively. Indexing AVA to BSA has been proposed to better evaluate AS severity with an indexed AVA (AVAi) ≤ 0.6 cm^2/m^2 used to identify severe AS [3, 5, 26]. While this approach may be useful in an individual patient to reconcile a discordant MG and AVA, using AVAi ≤ 0.6 cm^2/m^2 to define severe AS increases the prevalence of discordant hemodynamic indices and the prevalence of LG severe AS [6, 27–29]. In the SEAS trial, AVAi ≤ 0.6 cm^2/m^2 did not improve on the prediction of aortic valve events or cardiovascular death compared to AVA ≤ 1.0 cm^2 [28, 29]. Indexing to BSA appears to overcorrect for body size, and an AVAi ≤ 0.6 cm^2/m^2 is overly sensitive for severe AS, especially in obese patients where an AVAi < 0.5 cm^2/m^2 has been proposed to better identify severe AS [27]. Indexing AVA to height may be superior with an AVAi < 0.45cm^2/m

identifying patients at increased risk of a cardiovascular event [30•]. Indexing AVA to height is an attractive alternative as it would avoid the appearance of AS "regression" with weight loss.

Inherent Inconsistencies in the Definition of Severe AS in the Valve Guidelines

The valve guidelines implicitly state that an AVA of 1.0 cm^2 creates a MG of 40 mmHg (or Vmax of 4 m/s) as these are the thresholds for severe AS [3–5]. However, MG is dependent on SV and systolic ejection time, in addition to AVA. Under normal flow conditions, hemodynamic calculations would predict that an AVA of 1.0 cm^2 would create a MG of 30•–35 mmHg, rather than 40 mmHg. A MG as small as 26 mmHg can occur with an AVA of 1.0 cm^2 and normal hemodynamic parameters (cardiac output 6 L/min, heart rate 80 bpm, ejection time 330 ms) [31]. This inconsistency in the AVA, MG, and Vmax criteria for severe AS can result in LG severe AS.

Physiologic Causes for Low Gradient Severe AS

Low Flow Low Gradient Severe AS with a Reduced LV Ejection Fraction ("Classical Low Flow, Low Gradient AS")

The diagnostic criteria for low flow (LF), LG severe AS with a reduced LV ejection fraction (LVEF) include a MG < 40 mmHg, an AVA ≤ 1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2) and an LVEF < 50% [3–5]. While not explicitly stated in the AHA/ACC valve guidelines, [3] most studies have included criteria for LF, such as a SV index (SVi) < 35 ml/m^2 or a cardiac output < 3.0 $L/min/m^2$ [32]. The most recent guidelines from the American Society of Echocardiography (ASE) and the European Society of Cardiology (ESC) now include SVi < 35 ml/m^2 as diagnostic criteria [4, 5].

Classical LF-LG AS accounts for 5–10% of patients with severe AS [33•]. Although all patients have the same hemodynamic profile, they are a heterogeneous population [33•, 34, 35]. Some patients have anatomically severe disease, or "true-severe" AS, where-in the valve is severely stenotic and the LVEF is reduced due to afterload mismatch or concomitant myocardial disease (i.e., ischemic disease). Others have "pseudo-severe" AS, where there is only moderate anatomic disease, but AVA is in the severe range (i.e., ≤ 1.0 cm^2) due to low transvalvular flow and small opening forces being applied to the valve leaflets. Differentiating these two entities is important as the former group is likely to benefit from AVR, whereas the latter group may not benefit from AVR but may better benefit from therapies to improve ventricular function [36•, 37]. Depending on the criteria and technique used to identify true and pseudo-severe AS (surgical confirmation, stress echocardiography, MDCT aortic valve calcium (AVC) score), ≈ 30–40% of patients with classical LF-LG AS have "pseudo-severe" AS [33•, 38–40]. Although true-severe and pseudo-severe AS are usually thought of as two distinct entities, the contribution to which the valve and ventricular disease account for the hemodynamics varies between patients. Conceptually, the valve disease is dominant in true-severe AS, and the ventricular disease is dominant in pseudo-severe AS.

Distinguishing "True Severe" and "Pseudo-Severe" (Moderate) AS Low dose dobutamine stress echocardiography (DSE) plays an important role in distinguishing true and pseudo-severe AS [5, 33•, 41•]. However, DSE should only be performed after measurement error has been excluded as the cause for discrepant data. The rationale for DSE is to increase transvalvular flow and to reevaluate the hemodynamic indices at a normal flow state. Theoretically, patients with true-severe AS will have only a small change in AVA and a large increase in MG during flow augmentation. In contrast, patients with pseudo-severe AS will have a greater increase in AVA and only a small increase in MG with increased flow. Since the goal is to increase transvalvular flow, attempts should be made to avoid myocardial ischemia by using low dose infusions with gradual up-titrations. Dobutamine infusion is usually initiated at 2.5–5.0 μg/kg/min and increased 5 μg/kg/min every 5–8 min to 20 μg/kg/min [5, 33•, 41•]. LVOT velocity and transvalvular velocity are measured at rest and at each stage after a steady-state is achieved. LVOT diameter is measured at rest and is assumed constant throughout the test. SV, mean transvalvular flow rate (Qmean; stroke volume divided by the systolic ejection time), MG, and AVA should be calculated at each stage. The test should be stopped if the patient develops symptoms, blood pressure falls, or significant arrhythmias develop.

According to the AHA/ACC valve guidelines, true-severe AS is defined by a MG ≥ 40 mmHg with an AVA ≤ 1.0 cm^2 at any time during the test [3, 5]. However, a recent study in classical LF-LG AS revealed that these criteria have a poor sensitivity of 22%, a specificity of 81%, and a correct classification of only 47% for identifying true-severe AS [40•] (Fig. 2). The ESC valve guidelines suggest using a DSE peak AVA > 1.0 cm^2 to identify pseudo-severe AS; however, only 60% of patients were correctly classified using these criteria [40•].

A major confounder in distinguishing true and pseudo-severe AS by DSE relates to the variability to which flow augments during DSE. A significant proportion of patients never achieve a normal transvalvular flow rate (i.e., > 200–250 ml/s) and discordant data (MG < 40 mmHg, AVA ≤ 1.0 cm^2) persists. Others show a supranormal increase in flow

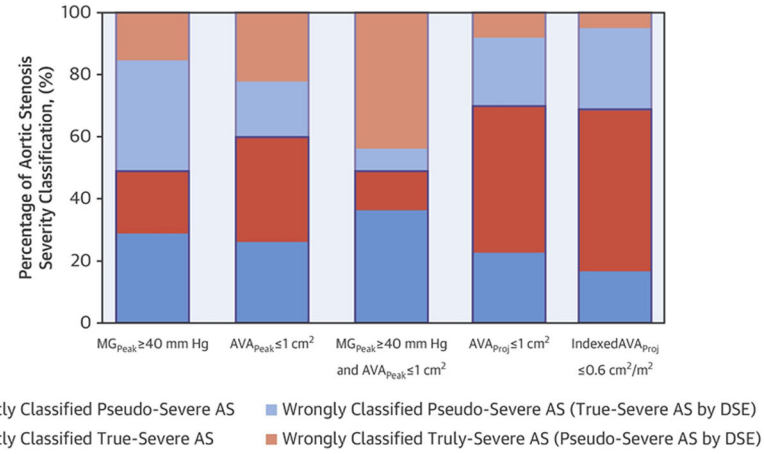

Fig. 2 Comparison of the correct classification of AS severity according to DSE criteria in 87 patients with LF-LF severe AS with reduced LVEF. Patients with true-severe (orange) and pseudo-severe AS (blue) based on surgical or CT confirmation are shown with the percent correct (dark color) or incorrect classification (light color) by DSE criteria. AS = aortic stenosis; AVA = aortic valve area; AVA_{proj} = projected aortic valve area at 250 ml/s; CT computed tomography; DSE = dobutamine stress echocardiography; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; MG = mean gradient. (Reprinted from Annabi et al.[40] with permission from Elsevier)

with a marked increase in MG and AVA and discordant HG AS (MG ≥ 40 mmHg, AVA > 1.0 cm^2).

An approach to address the inter-individual variability of flow responses during DSE is to calculate the projected AVA (AVAproj) at a standardized normal flow rate of 250 ml/s [38, 39]. AVAproj can be calculated by measuring AVA and Qmean at rest and at peak dobutamine dose using the formula [39]:

$$\mathrm{AVAproj} = \mathrm{AVArest} + [(\mathrm{AVApeak} - \mathrm{AVArest})/(\mathrm{Qpeak} - \mathrm{Qrest})] \times (250 - \mathrm{Qrest})$$

An AVAproj ≤ 1.0 cm^2 or an indexed AVAproj ≤ 0.55 cm^2/m^2 suggests the presence of true-severe AS, correctly classifying 70–95% of classical LF-LG AS patients with a performance superior to other DSE criteria [38–40] (Figs. 2 and 3). An important caveat is that an increase in flow is required to calculate AVAproj, and AVAproj may be unreliable if the flow increase is < 15% [38]. An important concept is that flow reserve, defined as a SV increase ≥ 20% with DSE [34], is not required to derive AVAproj. Although SV may increase very little or fall, shortening of the systolic ejection period can result in large increases in Qmean [40•].

In the small proportion of patients (11%) in whom the increase in Qmean is minimal (< 15%), [40•] alternate approaches using MDCT AVC score or the measurement of myocardial flow reserve with PET imaging can be used to distinguish true and pseudo-severe AS. An AVC score ≥ 2000 AU or > 500 AU/cm^2 in men, ≥ 1200 AU or > 300 AU/cm^2 in woman, or a myocardial flow reserve < 1.8 suggest the presence of true-severe AS [33•, 42].

Low Flow, Low Gradient Severe AS with Preserved LV Ejection Fraction (Paradoxical Low Flow, Low Gradient AS)

The diagnostic criteria for LF-LG severe AS with preserved LVEF include a Vmax < 4 m/s or MG < 40 mmHg, an AVA ≤ 1.0 cm^2, or AVAi ≤ 0.6cm^2/m^2, a SVi < 35 ml/m^2, but an LVEF ≥ 50% [3–5]. This entity accounts for 5–15% of AS patients with an AVA ≤ 1.0 cm^2 [43–46]. Conditions such as atrial fibrillation, severe hypertension, mitral regurgitation or stenosis, tricuspid regurgitation, right ventricular dysfunction, pulmonary artery hypertension, amyloidosis, and constrictive pericarditis can lead to a reduced SV and are frequently associated with this phenotype [43, 47–50]. This entity can also occur in isolation where it is referred to as paradoxical LF-LG severe AS. These patients are often elderly women and have small concentrically remodeled left ventricles or left ventricular hypertrophy and restrictive left ventricular physiology [44, 51]. Although LVEF is preserved, SV is reduced because of the small diastolic volume. LVEF underestimates LV dysfunction in concentrically remodeled ventricles, and there is frequently evidence of impaired LV contractility when assessed by global longitudinal strain (GLS), further accounting for the reduction in SV [45, 46]. Pathologic studies have shown increased myocardial fibrosis which may explain the abnormal GLS [52]. LV afterload, or valvuloarterial impedance (Zva, [MG+systolic BP]/SVi), is elevated due to reduced arterial compliance and is often equal to or greater than that observed with HG severe AS [44]. Supportive echocardiographic features such as reduced LV chamber size, concentric remodeling, impaired GLS,

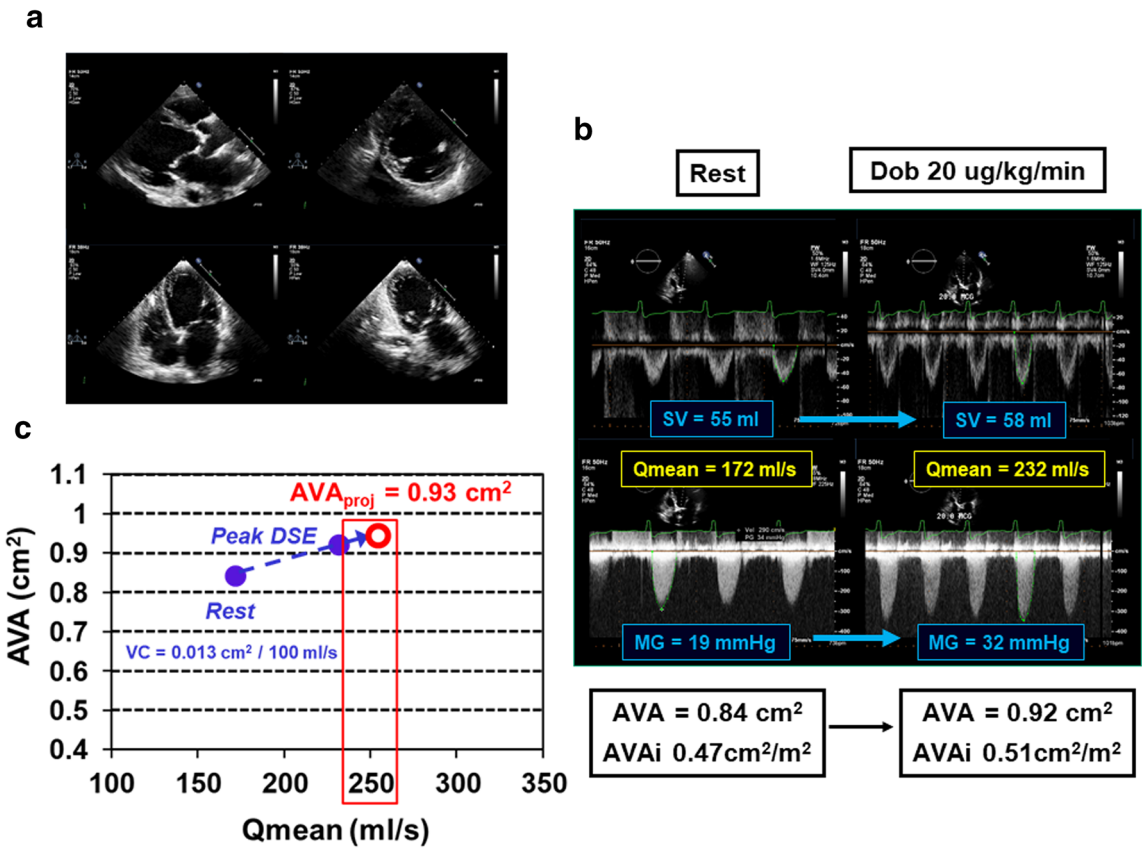

Fig. 3 Seventy-six-year-old man with LF-LG severe AS and an LVEF of 29% (**a**). Although SV increased minimally with DSE, Q_{mean} increased 35% due to shortening of the ejection time, but MG and AVA discordance persisted (**b**). AVAproj at a normal flow rate of 250 ml/s was calculated as AVAproj = rest AVA × VC × (250—rest Qmean), where VC = valve compliance or ΔAVA/ΔQmean (**c**). AVAproj confirmed the presence of true-severe AS. AVA = aortic valve area; AVAi = indexed aortic valve area; AVAproj = projected AVA at 250 ml/s; DSE = dobutamine stress echocardiography; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; MG = mean gradient; Qmean = mean transvalvular flow rate; SV = stroke volume; VC = valve compliance

and elevated Zva (> 5 mmHg/ml/m^2) should be sought, and the diagnosis questioned if these findings are absent.

Distinguishing "True Severe" and "Pseudo-Severe" (Moderate) AS As many as 30% of patients with LF-LG severe AS with preserved LVEF have moderate anatomic disease and pseudo-severe AS, a result of reduced transvalvular flow and flow-mediated valve opening forces [53]. Stress echocardiography with either exercise or dobutamine can be useful to distinguish true and pseudo-severe AS [54]. Although stress echocardiography may appear counterintuitive with a preserved LVEF, shortening of the ejection time can lead to a 40–50% increase in transvalvular flow despite little change in SV [54]. The presence of a MG ≥ 40 mmHg with an AVA ≤ 1.0 cm^2 during stress suggests the presence of true-severe AS, and an AVAproj ≤ 1 cm^2 or ≤ 0.55 cm^2/m^2 can be used to identify true-severe AS if transvalvular flow fails to normalize and discordant data persists (Fig. 4). In a small study with surgical confirmation, AVAproj ≤ 1.0 cm^2 or ≤ 0.55 cm^2/m^2 was 94% and 88% accurate for distinguishing true and pseudo-severe AS [54]. Recently, preload stress echocardiography using a leg massage machine to increase leg pressure has been employed to augment transvalvular flow [55•]. Although the augmentation of flow was modest (12% increase) compared with DSE, AVAproj derived using the two techniques showed a good correlation ($r = 0.94$). However, this technique may be inadequate in patients who have elevated filling pressures [56].

Normal Flow, Low Gradient Severe AS with Preserved LV Ejection Fraction

Normal flow (NF)-LG severe AS is defined by a Vmax < 4 m/s or MG < 40 mmHg, an AVA ≤ 1.0 cm^2 or AVAi ≤ 0.6 cm^2/m^2, a SVi > 35 ml/m^2, and an LVEF ≥ 50%. Although this entity is not described in the AHA/ACC valve guidelines [3], it is more common than LF-LG severe AS with a preserved LVEF and accounts for 15–30% of AS patients with an AVA ≤ 1.0 cm^2 [43, 45, 46]. This phenotype can result from [1] inherent inconsistencies in the definition of severe

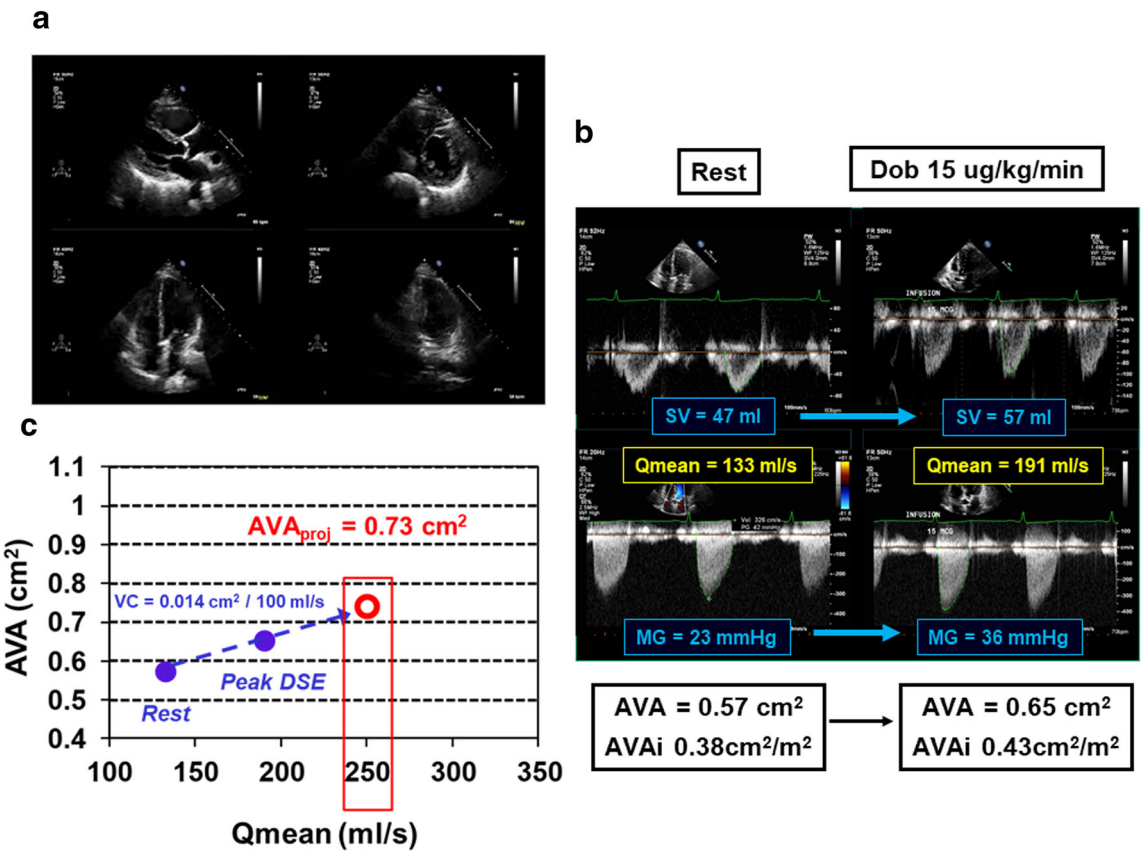

Fig. 4 Seventy-two-year-old woman with LF-LG severe AS with a preserved LVEF (**a**). SV and Qmean increased with DSE (21% and 44%, respectively, but MG and AVA discordance persisted (**b**). AVAproj at a normal flow rate of 250 ml/s was calculated at 0.73 cm^2 as described in Fig. 3 and confirmed the presence of true-severe AS(C). AVA = aortic valve area; AVAi = indexed aortic valve area; AVAproj = projected AVA at 250 ml/s; DSE = dobutamine stress echocardiography; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; MG = mean gradient; Qmean = mean transvalvular flow rate; SV = stroke volume; VC = valve compliance

AS in the valve guidelines [2], the presence of a low flow state (Qmean < 200 ml/s) that is not appreciated using SVi (≈ 25% of patients) [57] or [3], reduced arterial compliance with a predominantly flow-independent blunting of the MG by reflected pressure waves from the periphery [58].

Role of Stress Echocardiography in NF-LG Severe AS with Preserved LVEF Published studies on the utility of stress echocardiography in NF-LG severe AS with preserved LVEF are limited [55•, 59, 60]. In the subset of patients with a SVi > 35 ml/m^2 but reduced transvalvular flow < 200–250 ml/s, stress echocardiography makes conceptual sense as hemodynamic indices can be reevaluated at normal flow. In this situation, a MG ≥ 40 mmHg with an AVA ≤ 1.0 cm^2, or an EOAproj ≤ 1.0 cm^2 would highly suggest true-severe AS. In patients with a SVi > 35 ml/m^2 and normal transvalvular flow (> 200–250 ml/s), stress echocardiography is unlikely to provide additional incremental information as the AVA at a normal flow rate accurately reflects AS severity with a high positive predictive value of 84% [60].

Role of Echocardiography in Prognosis and Management of Low Gradient Severe AS

Low Flow Low Gradient Severe AS with a Reduced LV Ejection Fraction

The prognosis of patients with LF-LG severe AS with a reduced LVEF is poor with a mortality rate exceeding 40% at 2 years with medical therapy, but a historically high risk of morbidity and mortality with AVR [33•, 34•, 35•, 61–68]. Prognosis is largely dependent on [1] severity of the valve stenosis [2], ventricular function (and functional reserve), and [3] clinical factors such as concomitant comorbidities and the patient's functional capacity [35, 62, 68•, 69•]. In the multicenter TOPAS study, an AVAproj ≤ 1.0cm^2, but not resting AVA, was an independent predictor of increased mortality with conservative management (hazard ratio (HR) 3.78) [35, 40•]. Peak LVEF ≤ 35% with DSE, a composite of resting LVEF and contractile reserve, was also an independent predictor of mortality during conservative treatment (HR 2.61) [35]. In the European Multicenter study, lack of flow reserve,

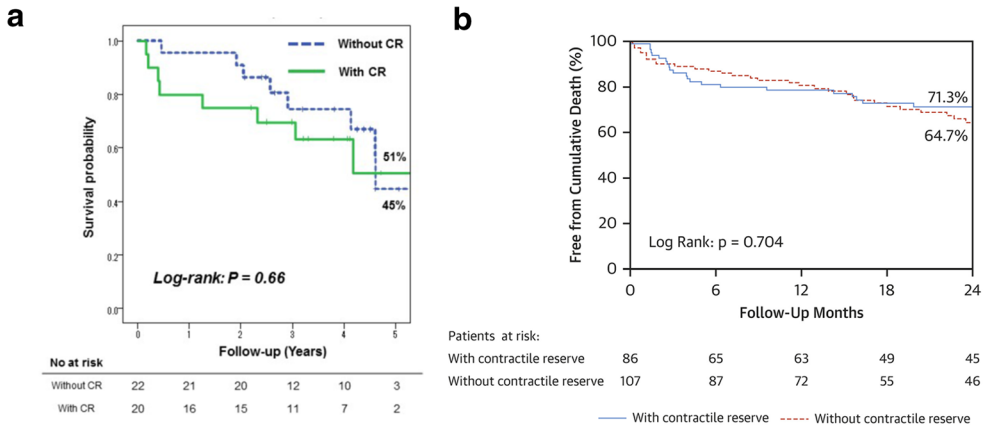

Fig. 5 Kaplan-Meier curves for all-cause mortality according to the presence of contractile (flow) reserve on DSE in patients with LF-LG severe AS with reduced LVEF undergoing surgical AVR ($n = 42$) (**a**) or TAVR ($n = 193$) (**b**). AS = aortic stenosis; AVR = aortic valve replacement, CR = contractile reserve; DSE = dobutamine stress echocardiography; LF = low flow; LG = low gradient. (Part A is reprinted from Sato K et al.[68] Part B is reprinted from Ribeiro et al.[69] with permission from Elsevier)

defined as an increase in SV < 20% with DSE, identified patients with a very poor survival with medical therapy, but also at very high risk with surgical AVR where 30-day mortality exceeded 30% [34, 62]. This latter data has guided patient management for years, but recent studies have questioned the prognostic value of flow reserve in the current era. Flow reserve did not predict outcome in the TOPAS study, [35] and recently, did not predict survival in 235 patients with classical LF-LG gradient AS who were managed conservatively or with surgical or transcatheter AVR [68•] (Fig. 5a). In the multicenter TOPAS–TAVI registry of 234 patients with classical LF-LG gradient AS undergoing DSE and transcatheter AVR, flow reserve did not predict survival at 30 days or 2 years [69•] (Fig. 5b). Furthermore, flow reserve did not predict their improvement in LVEF or functional status, similar to the initial observations from the European Multicenter study [69•, 70]. Newer measures of LV function, such GLS, may provide important additional information on the extent of myocardial impairment beyond LVEF and SVi. In the TOPAS study, absolute GLS < 9% was an independent predictor of mortality in patients managed medically (3-year survival, 34% vs. 55%) as well as undergoing AVR [71] (Fig. 6). Within the AVR group, the increased mortality observed with GLS < 9% predominantly resided in the first 30 days, thereby identifying a group at increased operative risk. Stress GLS may provide incremental prognostic information, and a DSE GLS < 10% has been proposed to identify patients at increased risk [71].

Attention to the right heart is critical as tricuspid regurgitation and right ventricular function are strongly associated with mortality independent of the treatment strategy [72, 73•]. In the TOPAS study, the presence of ≥ 2 + TR was an independent predictor of all-cause mortality (HR 1.88) [72]. Notably, in the subset undergoing AVR, 30-day mortality was 6.9% with ≤ 1 + TR, but 37% with ≥ 3 + TR (Fig. 7 a, b) Absolute

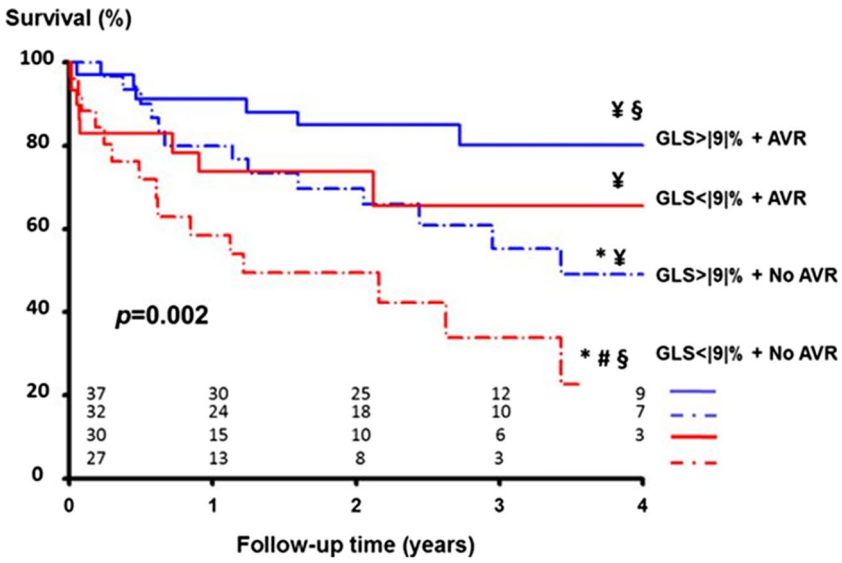

Fig. 6 Survival of patients with LF-LG severe AS($n = 126$) with reduced LVEF according to rest GLS and type of treatment. *$P < 0.05$ vs GLS > |9|% + AVR. #$P < 0.05$ vs GLS > |9|% + AVR, GLS < |9|% + AVR and GLS > |9|% + no AVR. §$P < 0.05$ vs GLS > |9|% + no AVR. ¥$P < 0.05$ vs GLS < |9|% + no AVR. AS = aortic stenosis; AVR = aortic valve replacement; GLS = global longitudinal strain; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction. (Reprinted from Dahou et al.[71] with permission of Wolters Kluwer)

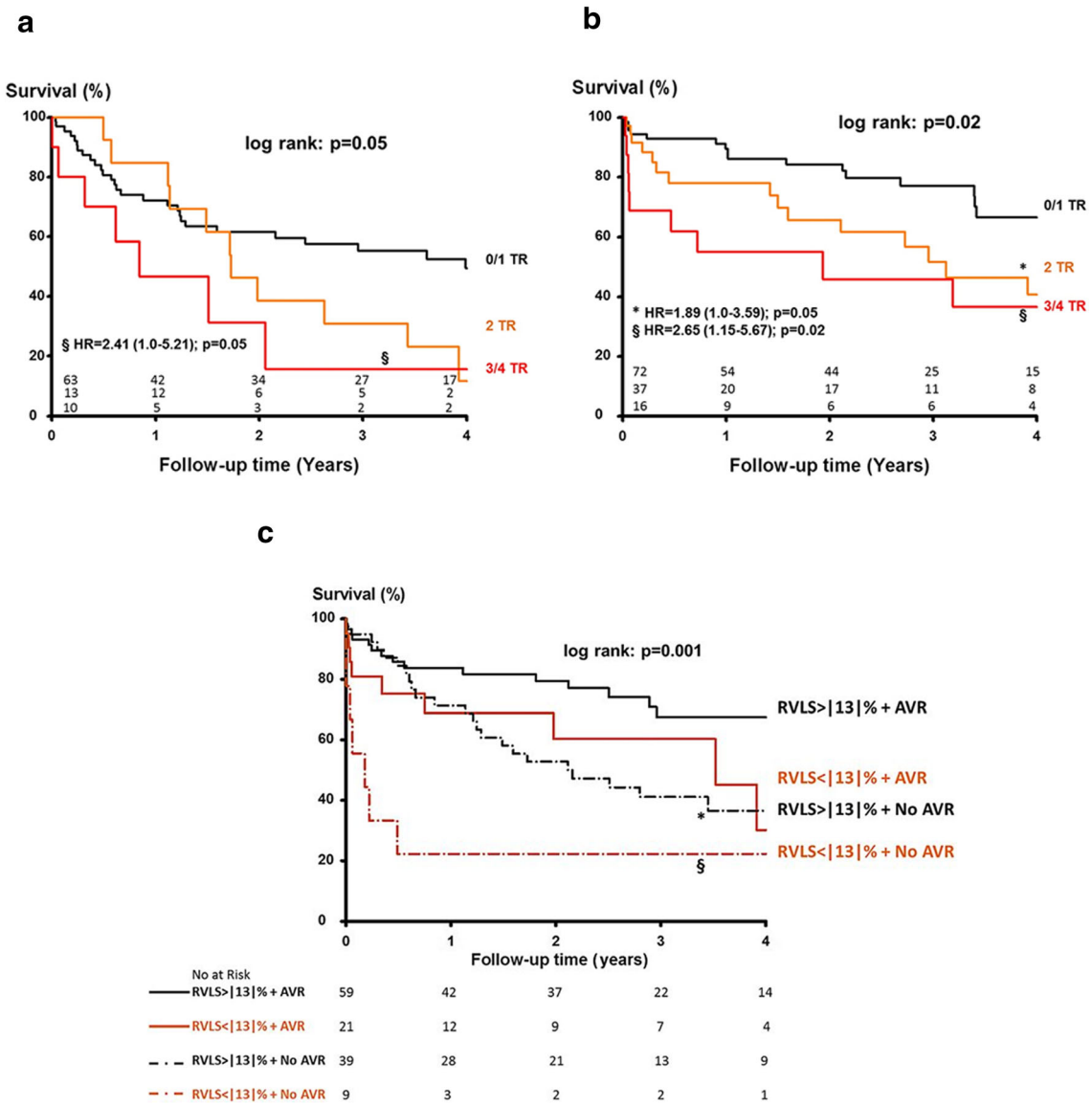

Fig. 7 Survival curve of LF-LG severe AS with reduced LVEF according to TR severity in 211 patients managed conservatively (**a**) or with AVR (**b**). Survival of 128 patients with LF-LG severe AS with reduced LVEF according to rest. RVLS and type of treatment (**c**). AS = aortic stenosis; AVR = aortic valve replacement; HR = hazard ratio; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; RVLS = right ventricular longitudinal strain; TR = tricuspid regurgitation. (Part A and B reprinted from Dahou et al.[72] with permission from Elsevier. Part C reprinted from Dahou et al.[73] with permission of BMJ Publishing Group)

right ventricular free wall longitudinal strain < 13% is associated with a 2.7-fold increased risk for all-cause mortality and is associated with a dismal prognosis with medical therapy [73•] (Fig. 7c). The prognostic value is incremental to baseline risk factors and LV GLS and maybe further enhanced by evaluating free wall strain under stress [73•].

In classical LF-LG AS with evidence of true-severe AS, the preponderance of studies show that surgical or transcatheter AVR is associated with better survival than medical management, and the LVEF and functional capacity improve in the majority of patients [34, 35, 62–64, 68•, 69•, 70•, 74–76]. Transcatheter AVR, preferable transfemoral AVR, appears to be the preferred strategy with a recent large multicenter registry demonstrating 30-day mortality of only 3.8%, much lower than predicted by the STS score and previous surgical series [69•]. However, approximately one-third of patients are dead 2 years post-transcatheter AVR. Furthermore, anatomic/procedural specific impediments and coronary artery considerations may necessitate other AVR approaches [33•, 69•, 77]. Thus, echocardiographic prognostic markers continue to have an important role in the decision-making on valve intervention in individual patients.

Controversy exists as to the best management strategy for patients with pseudo-severe LF-LG AS with a reduced LVEF [36•]. Current guidelines do not recommend AVR [3–5]. However, while some studies have suggested that the

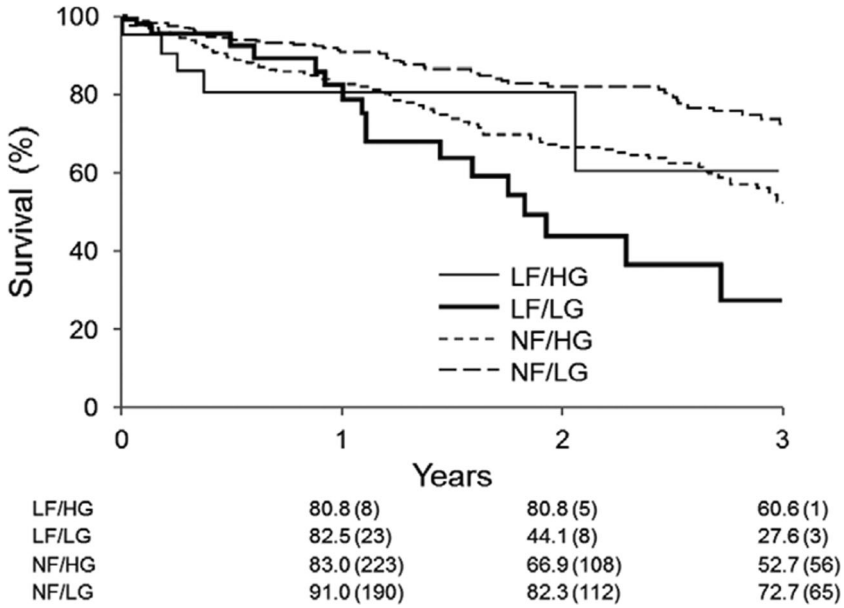

Fig. 8 Survival of 1704 medically managed severe AS patients with LVEF > 50% (censored at AVR) based on the flow - pressure gradient classification. The LF-LG group had the worst survival and the NF-LG group had the best survival ($p < 0.0001$). AVR = aortic valve replacement; HG = high gradient; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; NF = normal flow. (Reprinted from Eleid et al.[43] with permission from Wolters Kluwer)

prognosis of these patients is similar to systolic heart failure in the absence of AS [37], other have suggested a worse prognosis and that AVR may be beneficial [36•, 68•, 78]. The ongoing TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure) trial is enrolling these patients and will provide insight into the optimal management [36•].

Low Flow, Low Gradient Severe AS with Preserved LV Ejection Fraction

Paradoxical LF-LG severe AS has the worst prognosis of the four flow-pressure gradient patterns of severe AS with normal LVEF [43, 46, 79] (Fig. 8). SVi is a strong independent predictor of clinical outcome and survival worsens as SVi declines [80–82]. In patients with LG severe AS with normal LVEF in the SEAS trial (≈ 50% with LF), MG was the strongest independent predictor of aortic valve events, and the addition of AVA or VR did not improve on the prediction of events [83]. In 55 patients with paradoxical LF-LG AS, a large proportion with symptoms or equivocal symptoms, the need for AVR or death at 1 year approached 50% in patients with AVAproj ≤ 1.0 cm^2 or ≤ 0.55 cm^2/m^2 vs. < 10% if AVAproj was > 1.0 cm^2 or > 0.55 cm^2/m^2 [54] (Fig. 9). A higher threshold of AVAproj < 0.72 cm^2/m^2 for predicting cardiac events has been reported in a group of asymptomatic or equivocally symptomatic patients [55•]. GLS is frequently abnormal and can provide prognostic information [45, 46, 84]. An absolute GLS ≤ 17% was associated with a 2-year event-free survival of only 57% vs. 97% if GLS > 17%, suggesting a population who require closer monitoring [84].

Patients with LF-LG severe AS with preserved LVEF have increased surgical risks; however, their outcome is improved with surgical or transcatheter AVR [44, 74, 76•, 79]. The ACC/AHA and ESC guidelines recommend considering AVR in symptomatic patients if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms [3, 5]. In this regard, we believe that true-severe AS should be confirmed with either DSE or MDCT AVC score prior to proceeding with AVR.

Normal Flow, Low Gradient Severe AS with Preserved LV Ejection Fraction

Patients with NF-LG severe AS have a prognosis similar to patients with moderate AS, at least in the initial 2 years [43, 85•]. MG and SVi appear to be important predictors of outcome in this population [80, 83]. Although SVi ≤ 35 ml/m^2 is used to define LF, patients with SVi of 35–43 ml/m^2 also have reduced survival compared with patients with SVi > 43 ml/m^2 [80]. Low transvalvular flow rate < 200 ml/s can be seen despite a SVi > 35 ml/m^2, and is associated with higher rates of cardiovascular and all-cause mortality and may better predict outcome than SVi [57].

While some studies have suggested that AVR does not improve survival in NF-LG severe AS compared with conservative management when patients have mild symptoms [43, 86], a large meta-analysis suggests a benefit of AVR [79]. New indices, such as the "Relative Valve Load", or MG/Zva, which describes the relative contribution of the valvular load to the global LV load, may better predict who is likely to benefit from AVR [87]. In our opinion, patients who are clearly symptomatic with NF-LG severe AS, and confirmed to have true-severe AS by DSE or MDCT AVC score, should undergo valve intervention with either transcatheter or

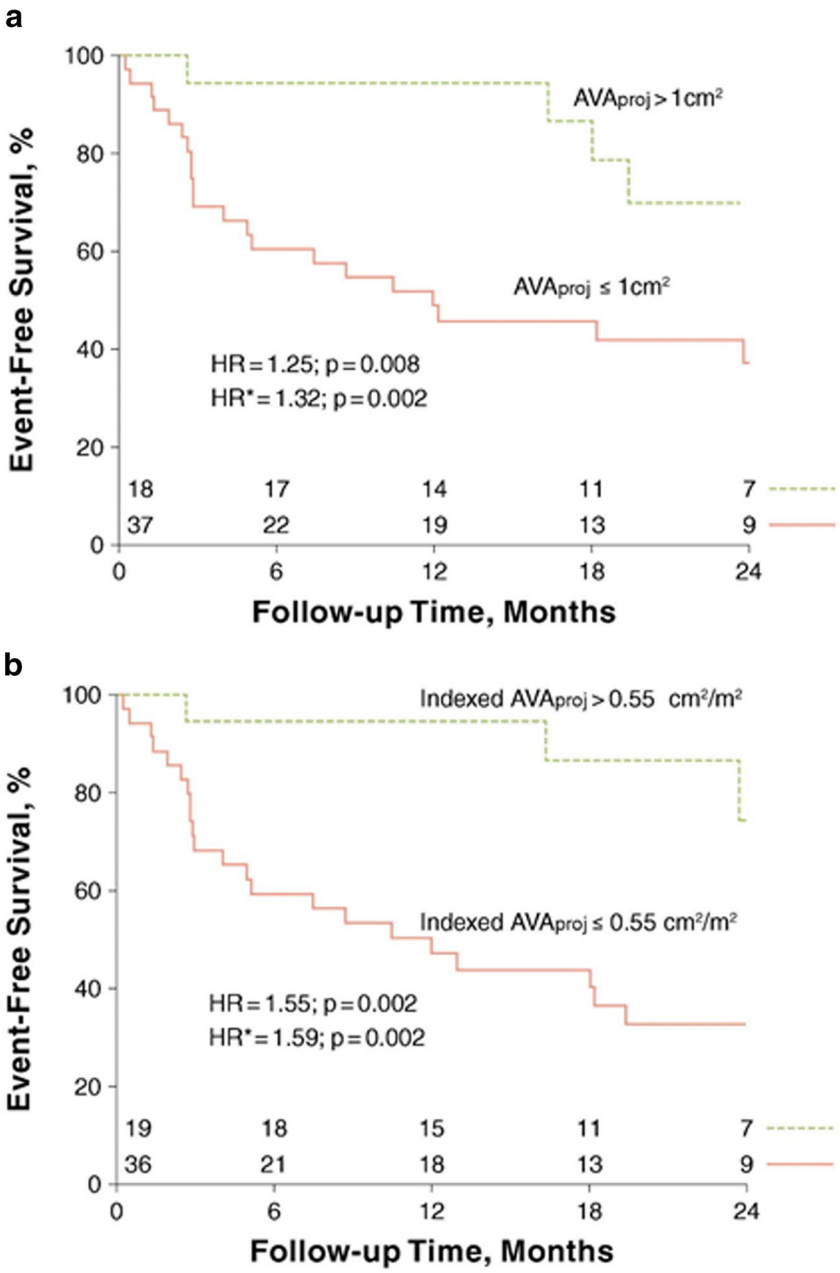

Fig. 9 Event free-survival of 55 patients with LF-LG severe AS with preserved LVEF based on AVAproj (**a**) and indexed AVAproj (**b**). AVA_{proj} = projected aortic valve area at 250 ml/s; HR = hazard ratio. (Reprinted from Clavel et al.[54] with permission of Elsevier)

surgical AVR depending on patient-specific clinical, anatomic, vascular, and coronary artery disease factors.

Conclusion

Patients with LG severe AS are commonly encountered in the echocardiography laboratory and present a diagnostic and management dilemma. Echocardiography plays a pivotal role in these patients, providing insight into the reason for the discordant hemodynamics, confirming the severity of AS, and providing important prognostic information to guide management decisions. A systematic comprehensive approach that often incorporates the modalities of transthoracic, transesophageal and stress echocardiography is required to optimally evaluate and manage these patients.

Compliance with Ethical Standards

Conflict of Interest Ian G. Burwash has no conflict of interest to declare.
David Messika-Zeitoun reports grants and personal fees from Edwards Lifesciences.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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