

## Clinical update

# Low-gradient aortic stenosis

Marie-Annick Clavel<sup>1</sup>, Julien Magne<sup>2</sup>, and Philippe Pibarot<sup>1\*</sup>

<sup>1</sup>Québec Heart and Lung Institute/Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, 2725 Chemin Sainte Foy, #A-2075, QC, Canada G1V4G5; and <sup>2</sup>CHU Limoges, Hôpital Dupuytren, Faculté de médecine de Limoges, Limoges, France

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An important proportion of patients with aortic stenosis (AS) have a ‘low-gradient’ AS, i.e. a small aortic valve area (AVA < 1.0 cm<sup>2</sup>) consistent with severe AS but a low mean transvalvular gradient (< 40 mmHg) consistent with non-severe AS. The management of this subset of patients is particularly challenging because the AVA-gradient discrepancy raises uncertainty about the actual stenosis severity and thus about the indication for aortic valve replacement (AVR) if the patient has symptoms and/or left ventricular (LV) systolic dysfunction. The most frequent cause of low-gradient (LG) AS is the presence of a low LV outflow state, which may occur with reduced left ventricular ejection fraction (LVEF), i.e. classical low-flow, low-gradient (LF-LG), or preserved LVEF, i.e. paradoxical LF-LG. Furthermore, a substantial proportion of patients with AS may have a normal-flow, low-gradient (NF-LG) AS: i.e. a small AVA—low-gradient combination but with a normal flow. One of the most important clinical challenges in these three categories of patients with LG AS (classical LF-LG, paradoxical LF-LG, and NF-LG) is to differentiate a true-severe AS that generally benefits from AVR vs. a pseudo-severe AS that should be managed conservatively. A low-dose dobutamine stress echocardiography may be used for this purpose in patients with classical LF-LG AS, whereas aortic valve calcium scoring by multi-detector computed tomography is the preferred modality in those with paradoxical LF-LG or NF-LG AS. Although patients with LF-LG severe AS have worse outcomes than those with high-gradient AS following AVR, they nonetheless display an important survival benefit with this intervention. Some studies suggest that transcatheter AVR may be superior to surgical AVR in patients with LF-LG AS.

### Keywords

Aortic stenosis • Low flow • Low gradient • Echocardiography • Computed tomography • Aortic valve replacement • Transcatheter aortic valve replacement

## Introduction

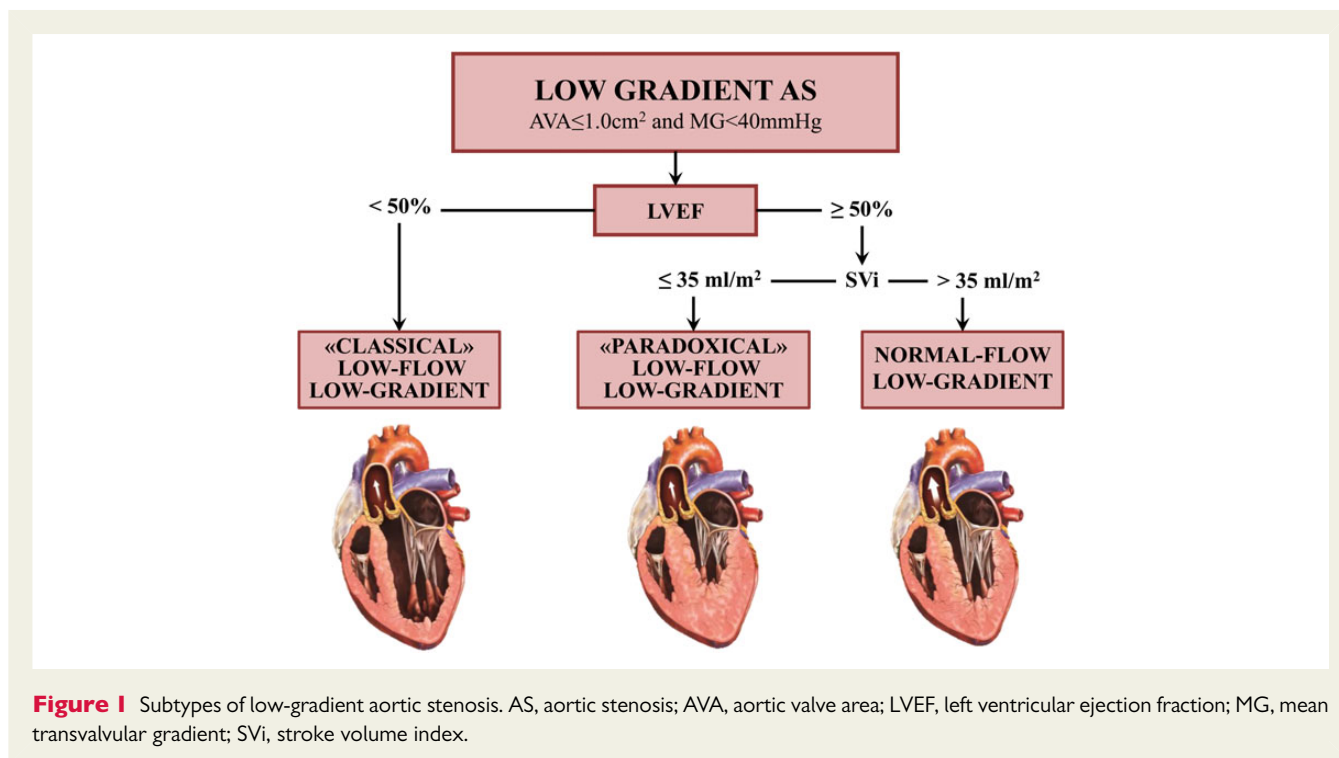
Aortic stenosis (AS) is the most frequent valvular heart disease and the most frequent cause of valve procedure. There is currently no pharmacological therapy available to reduce the progression of AS and aortic valve replacement (AVR) is thus the only available treatment for this disease. During the past decade, transcatheter aortic valve replacement (TAVR) as emerged as an alternative to surgical aortic valve replacement (SAVR).

The therapeutic management of AS is essentially determined by: (i) the severity of the stenosis; (ii) the patient’s symptomatic status, and (iii) the status of LV systolic function. Severe AS is defined as a peak aortic jet velocity  $\geq 4$  m/s, a mean transvalvular pressure gradient  $\geq 40$  mmHg, and/or an aortic valve area (AVA) < 1.0 cm<sup>2</sup>. Doppler-echocardiography is the primary modality for the assessment and follow-up of stenosis severity and LV function. The 2012 ESC-EACTS guidelines<sup>1</sup> and 2014 ACC-AHA guidelines<sup>2</sup> recommend AVR (Class I indication) in patients with high-gradient (mean gradient  $\geq 40$  mmHg) severe AS who have symptoms, LV

systolic dysfunction defined as a left ventricular ejection fraction (LVEF) < 50%, and/or undergo another cardiac surgery. However, an important proportion (up to 50%) of patients with AS have a ‘low-gradient’ AS, i.e. a small AVA (< 1.0 cm<sup>2</sup>) consistent with severe AS but a low-gradient (< 40 mmHg) consistent with non-severe AS. The management of this subset of patients is particularly challenging because the AVA-gradient discrepancy raises uncertainty about the actual stenosis severity and thus about the indication of AVR if the patient has symptoms or LVEF < 50%. The most frequent cause of low-gradient (LG) AS is the presence of a low LV outflow state, which may occur with reduced LVEF, i.e. classical low flow, or preserved LVEF, i.e. paradoxical low flow. Low flow is defined in the guidelines as a stroke volume index < 35 mL/m<sup>2</sup> and is present in up to 35% of patients with AS (Figure 1).<sup>3–10</sup> The transvalvular pressure gradient is highly flow-dependent (i.e. a squared function of flow) and may thus be ‘pseudo-normalized’ and underestimate stenosis severity in presence of low flow. On the other hand, the AVA may be pseudo-severe due to incomplete opening of the valve orifice and may thus overestimate stenosis severity.

\* Corresponding author. Tel: +1 418 656 8711 ext. 5938, Fax: +1 418 656 4918, Email: [philippe.pibarot@med.ulaval.ca](mailto:philippe.pibarot@med.ulaval.ca)

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**Figure 1** Subtypes of low-gradient aortic stenosis. AS, aortic stenosis; AVA, aortic valve area; LVEF, left ventricular ejection fraction; MG, mean transvalvular gradient; SVi, stroke volume index.

Of note, a low-flow state does not necessarily imply the presence of low gradient and some patients with very severe AS may have low flow and still a high gradient (mean gradient >40 mmHg). Furthermore, a substantial proportion of patients with AS may have a low gradient but with a normal flow (stroke volume index >35 mL/m<sup>2</sup>) (Figure 1). This entity is often referred as to normal-flow, LG AS. Hence, three main subtypes of LG AS can be identified depending on the values of LVEF and flow:<sup>5,11</sup> (i) classical (low LVEF) low-flow, low-gradient (LF-LG) AS, (ii) paradoxical (preserved LVEF) LF-LG AS, and (iii) normal flow-LG (NF-LG) AS (Figure 1). These three entities are all characterized by the conjunction of a small AVA and low gradient and pose major challenges for the diagnosis and therapeutic decision making. The purpose of this article is to provide a state-of-the-art review of the clinical management for these three subtypes of LG AS.

## Technical pitfalls and measurement errors

The finding of a LG AS at echocardiographic exam may be related to an error in the echocardiographic measurement of the AVA or gradient. The first step when confronted to the combination of a small AVA with a low gradient at Doppler-echocardiographic exam is thus to rule-out measurement errors. In order to obtain accurate measurement of peak aortic jet velocity and mean gradient, it is important to perform a multi-window interrogation and align the continuous-wave Doppler beam with the direction of aortic flow jet (see Supplementary material online).<sup>12</sup> The AVA is even more prone than the mean gradient to measurement errors, particularly in the elderly patient with a calcified aortic valve. The AVA is determined by the continuity equation method where the numerator is the

stroke volume measured in the LV outflow tract (LVOT) and the denominator is the time-velocity integral of the aortic flow.<sup>13</sup> Given that the LVOT diameter is squared in the continuity equation, a small error in this measure may result in an important error in the calculation of the AVA (see Supplementary material online).

## Classical (Reduced Left Ventricular Ejection Fraction) Low-Flow, Low-Gradient Aortic Stenosis

### Definition and pathophysiology

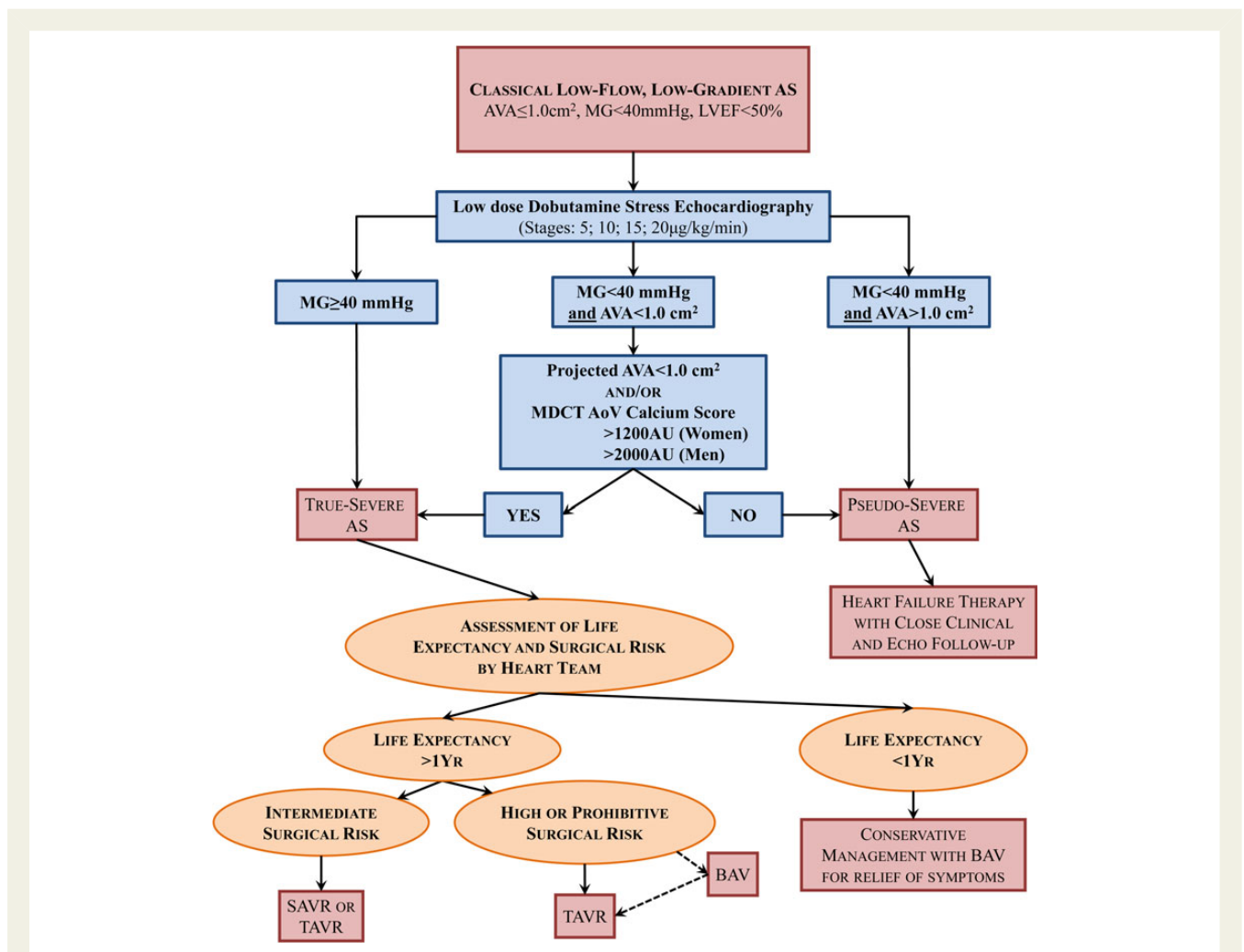
Classical LF-LG AS is defined in the guidelines as an AVA <1.0 cm<sup>2</sup>, a mean gradient <40 mmHg, and an LVEF <50% (Figure 1).<sup>12</sup> Although this is not always the case, this definition assumes that a low LVEF is associated with low LV outflow. In these patients, the low-flow state is predominantly due to depressed LV systolic dysfunction, which may be related to the presence of severe AS and ensuing LV afterload mismatch and/or to the presence of concomitant cardiomyopathy, most frequently from ischaemic origin. Classical LF-LG AS shares several pathophysiological and clinical similarities with reduced-LVEF heart failure. This entity is found in ~5–10% of the AS population and is associated with worse outcomes compared with patients with high-gradient AS and/or preserved LVEF.<sup>14–17</sup>

### Stenosis severity

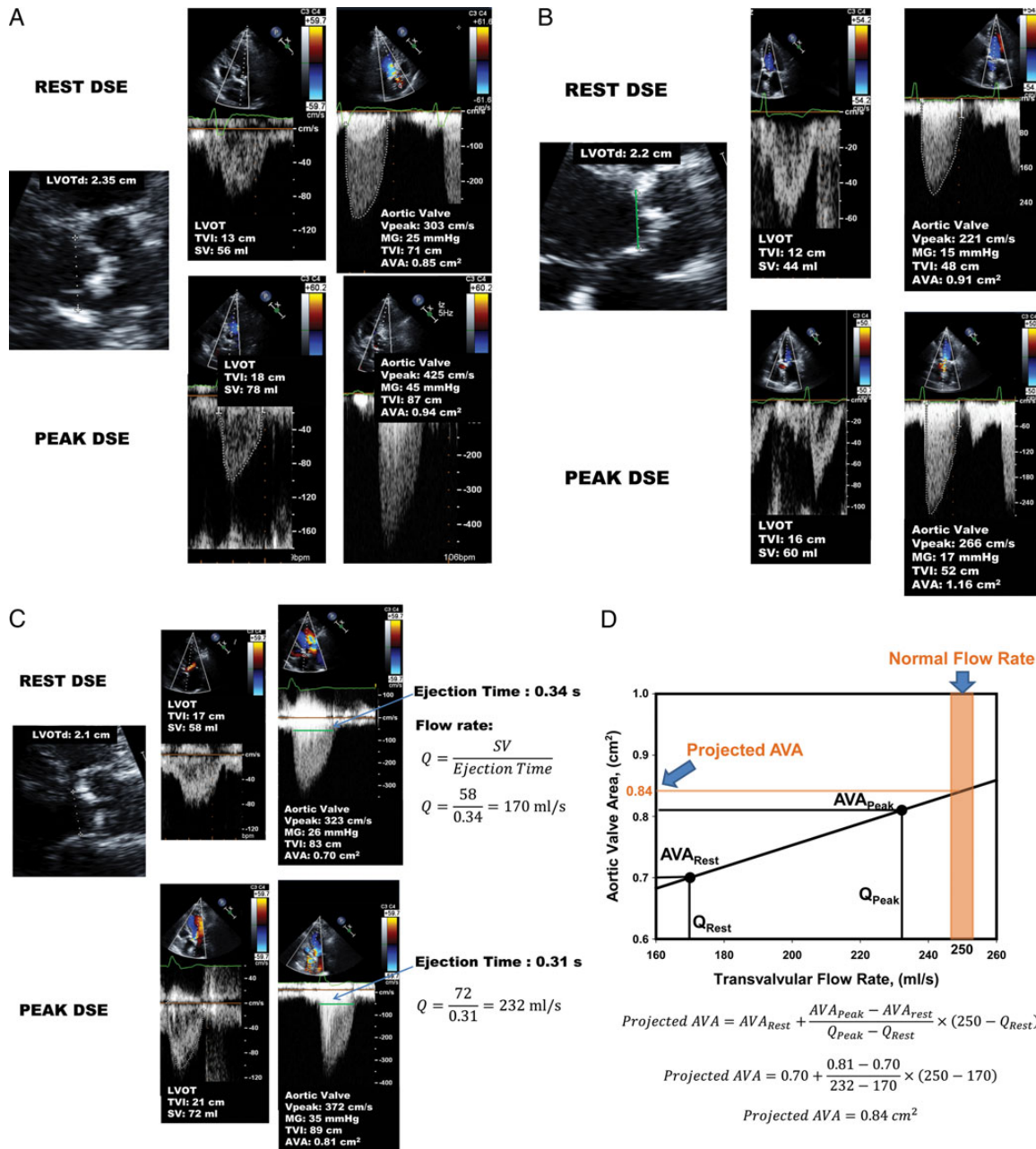
One of the main diagnostic challenges in LF-LG AS is to differentiate a true-severe AS that generally benefits from AVR vs. a pseudo-severe AS (i.e. non-severe AS with incomplete valve opening) that may not benefit from this intervention. A low-dose dobutamine

stress echocardiography (DSE) is recommended to confirm stenosis severity and assess LV flow reserve (Figures 2 and 3).<sup>1,2,18–21</sup> The DSE protocol differs from that used for the detection of ischaemic heart disease in the sense that the maximum target dose is lower: 20 µg/kg/min (vs. 40 µg/kg/min) and the duration of each dose stage (5, 10, 15, and 20 µg/kg/min) is longer: 5–8 min (vs. 3 min) to allow measurements of stroke volume, gradient, and AVA in a stable, steady-state, haemodynamic condition. It is recommended to hold β-blocker medication, if any, on the day of DSE, when physician considers it safe.<sup>22</sup> The stenosis is considered true-severe when the mean gradient is ≥40 mmHg with an AVA being generally <1.0 cm<sup>2</sup> at any of the DSE stages (Figures 2 and 3A).<sup>1,2</sup> On the other hand, pseudo-severe AS is characterized by a stress mean gradient <40 mmHg and a stress AVA >1.0 cm<sup>2</sup> (Figures 2 and 3B). The inter-individual flow response to DSE varies extensively depending on the degree of stenosis severity and the presence of LV afterload mismatch and/or concomitant cardiomyopathy. About one-third of patients with classical LF-LG AS have no LV flow reserve, which is defined as a per cent increase in stroke

volume <20% during DSE.<sup>20,21</sup> These patients have high surgical risk<sup>19,23,24</sup> and, because of the absence of flow increase, the stenosis severity often remains indeterminate with DSE (Figure 3E).<sup>18</sup> Among the patients with significant flow reserve on DSE, some exhibit complete normalization of transvalvular flow, whereas others only have modest increase in flow and thus remain below the normal flow range. In the latter subset, the small AVA-low-gradient pattern and thus the uncertainty about stenosis severity may persist at DSE. In such patients, it is useful to calculate the projected AVA at normal flow rate (Figures 2 and 3C and D).<sup>20,21</sup> This parameter provides an estimate of what would be the AVA had the patient reached normal flow rate with DSE (Figure 3D). A projected AVA <1.0 cm<sup>2</sup> suggests the presence of true-severe AS. However, a minimum of 15% increase in mean transvalvular flow rate (stroke volume/LV ejection time) is required to ensure reliable assessment of the projected AVA. Some studies suggest that larger cut-point value (i.e. <1.2 cm<sup>2</sup> instead of <1.0 cm<sup>2</sup>) of stress AVA and projected AVA and/or lower cut-point value of stress mean gradient (>30 mmHg instead of >40 mmHg) should be used to



**Figure 2** Algorithm for the management of classical (reduced left ventricular ejection fraction) low-flow, low-gradient aortic stenosis. AoV, aortic valve; BAV, balloon aortic valvuloplasty; MDCT, multi-detector computed tomography; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement. Other abbreviations as in Figure 1.

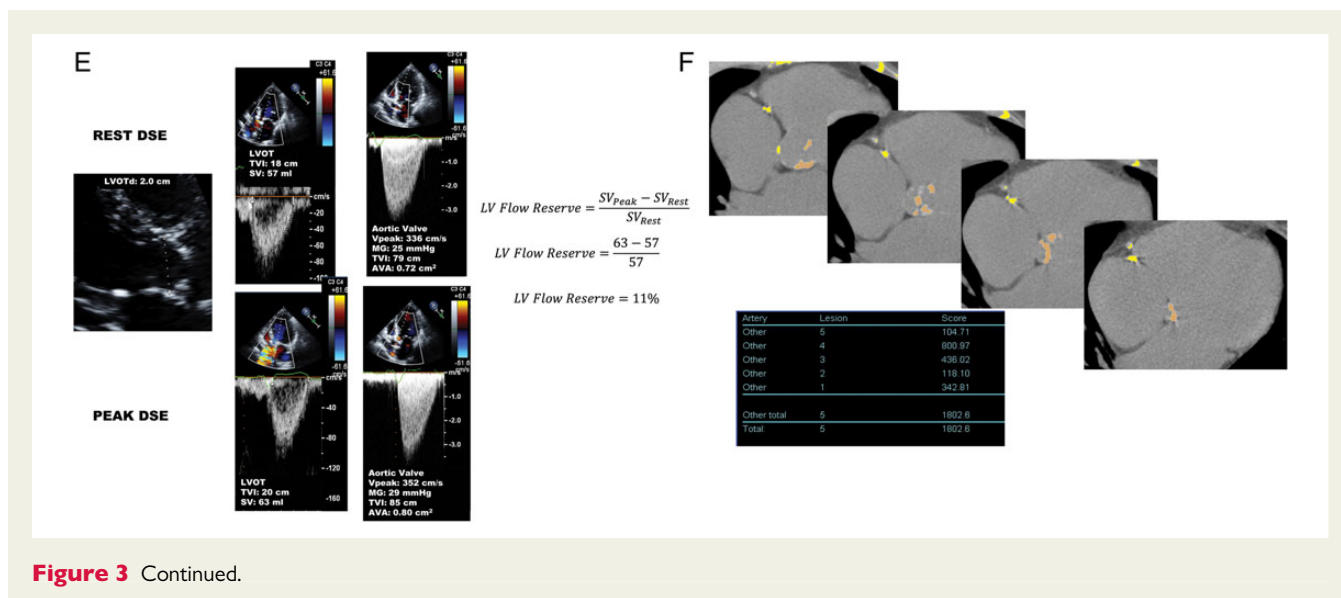


**Figure 3** Dobutamine stress echocardiography for the assessment of stenosis severity in classical (reduced left ventricular ejection fraction), low-flow, low-gradient aortic stenosis. (A) Patient with true-severe aortic stenosis; (B) patient with pseudo-severe aortic stenosis; (C and D) patient with persisting discordant grading (i.e. small aortic valve area with low mean transvalvular gradient) at dobutamine stress echocardiography (C) and calculation of the projected aortic valve area at normal flow rate (0.84 cm<sup>2</sup>) to confirm the presence of severe stenosis in this patient (D). (E and F) Patient with no left ventricular flow reserve on dobutamine stress echocardiography and measurement of aortic valve calcification score by multi-detector computed tomography to confirm stenosis severity. This patient is a woman and has a calcium score of 1802 AU, which is consistent with true-severe aortic stenosis (see Figure 4). DSE, dobutamine stress echocardiography; LVOT, LV outflow tract; LVOTd, LVOT diameter; TVI, time-velocity integral; SV, stroke volume; SV<sub>Rest</sub>, SV at rest; SV<sub>Peak</sub>, SV at peak DSE; Q, mean transvalvular flow rate (SV/ LV ejection time); V<sub>Peak</sub>, peak aortic jet velocity. Other abbreviations as in Figures 1 and 2.

identify true-severe stenosis and consider AVR.<sup>21,25</sup> This suggestion is based on the rationale that a patient with a depressed systolic LV function may be more vulnerable to the increased LV afterload related to AS and that a moderate AS may thus represent a severe

haemodynamic burden for a patient with decompensated LV function.

In the patients with no significant increase in flow rate (<15%), it is often impossible to differentiate true- vs. pseudo-severe AS by



**Figure 3** Continued.

DSE (Figure 3E) and, in these patients, the quantitation of the degree of aortic valve calcification by multi-detector computed tomography (MDCT) may be used to corroborate stenosis severity (Figures 2, 3F, and 4). The amount of aortic valve calcification may indeed accurately be quantitated by MDCT using the modified Agatston method (Figure 4). The aortic valve calcification score has been shown to predict AS haemodynamic severity as well as the rate of stenosis progression and the occurrence of adverse events.<sup>26–28</sup> Lower cut-point values of aortic valve calcium score should be used in women ( $\geq 1200$  AU) vs. in men ( $\geq 2000$  AU) to distinguish true-severe from pseudo-severe AS (Figure 4).<sup>26–28</sup> In patients with small or large aortic annuli, the aortic valve calcium score should be indexed for the cross-sectional area of the aortic annulus to calculate the ‘aortic valve calcium density’. Values of valve calcium density  $\geq 300$  AU/cm<sup>2</sup> and  $\geq 500$  AU/cm<sup>2</sup> are consistent with true-severe AS in women and men, respectively.<sup>26–28</sup> One limitation of MDCT is that it only measures the valvular calcification but not the valvular fibrosis, which may also contribute to the stenosis. For that reason, this modality may yield to false-negative results in younger patients with bicuspid AS. However, such patients are rare in the LF-LG AS population.

Cardiac catheterization for haemodynamic assessment of AS is only recommended in symptomatic patients when there are uncertainties or discrepancies among the non-invasive parameters of stenosis severity.<sup>1,2</sup> However, in low-flow state conditions, rest cardiac catheterization does not provide any additional information on stenosis severity or LV function besides that obtained by rest echocardiography. Dobutamine stress catheterization can be used to differentiate TS from PS AS and assess the presence of LV flow reserve<sup>29</sup> but it is more invasive than DSE and is also subject to technical pitfalls and measurement errors (see Supplementary material online).

## Outcomes and risk stratification

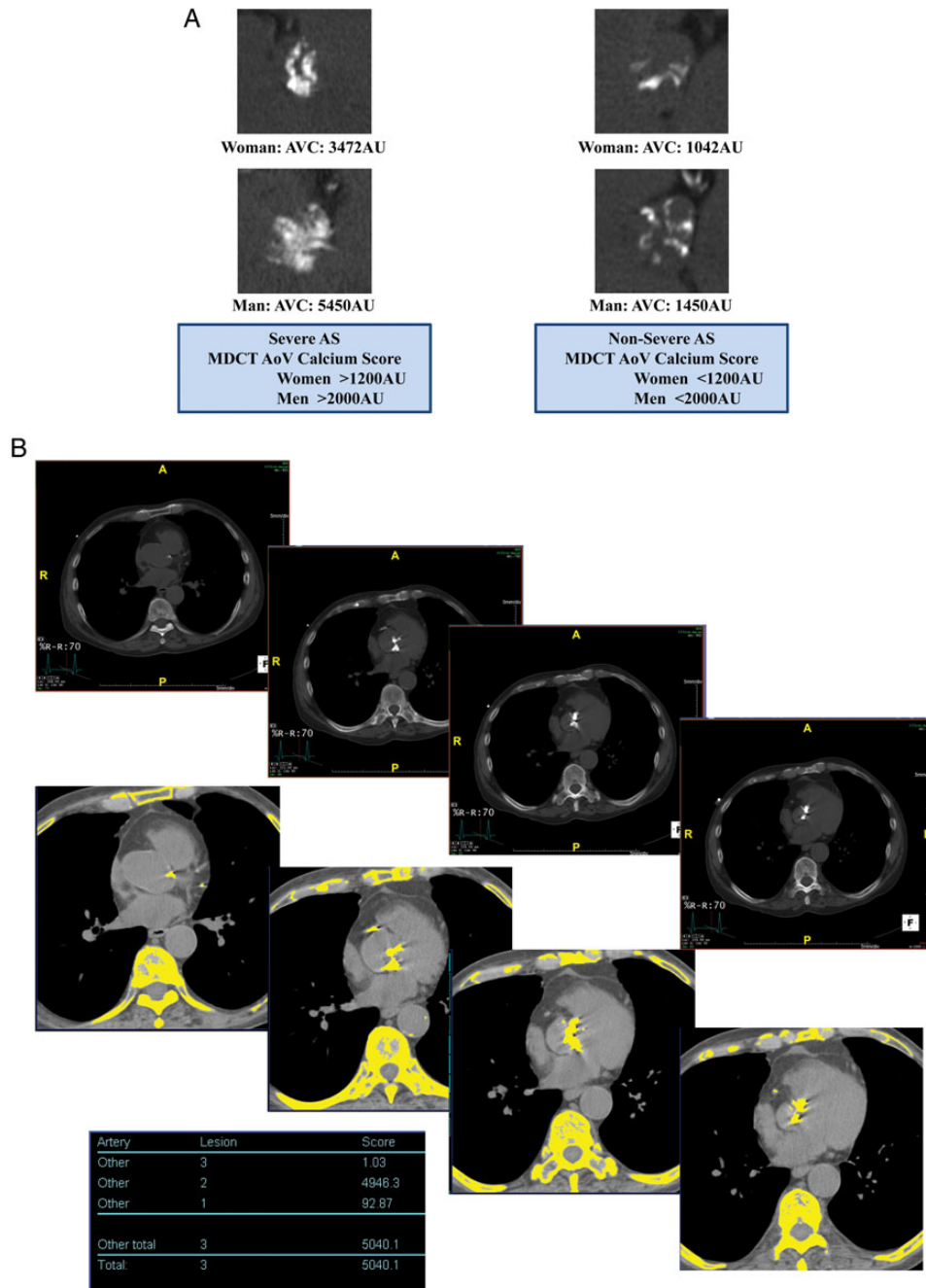
The classical LF-LG AS is one of the subsets of the AS population that has the highest risk of mortality and adverse events. The survival rate of these patients is low (40–60% at 2-year) with

conservative management but the 30-day mortality with SAVR is high (8–33%).<sup>15,19,23–25,29–36</sup> Nevertheless, despite the high surgical risk, SAVR is associated with major survival benefit compared with conservative management in patients with classical LF-LG severe AS.<sup>24,32,35</sup> Patients with pseudo-severe AS have better survival than patients with true-severe AS or those with no LV flow reserve treated conservatively.<sup>37</sup>

Once the presence of severe AS and thus the indication for AVR are confirmed, careful assessment of surgical risk and post-AVR estimated life expectancy by the Heart Team is crucial to select the most appropriate modality of treatment, i.e. SAVR vs. TAVR vs. conservative management, for the given patient (Figure 2).<sup>1,2</sup> The main factors that have been associated with increased risk of mortality under conservative management as well as after AVR in patients with classical LF-LG AS include: (i) severe functional impairment defined as NYHA class  $\geq$  III, 6-min walk test distance  $< 320$  m, and/or Duke activity score index  $< 20$ , (ii) the presence of multi-vessel coronary artery disease; (iii) very low LVEF: i.e.  $< 35\%$  at rest or at DSE; (iv) severe impairment of LV longitudinal systolic function at rest and at DSE: i.e. LV global longitudinal strain measured by speckle tracking imaging  $< 9\%$  and  $< 10\%$ , respectively; (v) the absence of LV flow reserve on DSE; (vi) moderate-to-severe stenosis defined as a projected AVA  $< 1.2$  cm<sup>2</sup>; (vii) Moderate/severe tricuspid regurgitation; (viii) marked elevation of circulating levels of B-type natriuretic peptides (BNP  $> 550$  pg/mL or NT-pro BNP  $> 3950$  pg/mL); and (ix) higher degree of myocardial fibrosis at cardiac magnetic resonance imaging.<sup>15,19,24,25,29,30,35,38–40</sup>

In the subset of patients undergoing AVR, pre-operative NYHA class  $\geq$  III, mean gradient  $< 20$  mmHg, LVEF  $< 35\%$ , global longitudinal strain  $< 9\%$ , the presence of multi-vessel coronary disease, the absence of flow reserve on DSE, and higher logistic EuroSCORE or STS score are associated with increased risk of perioperative mortality.<sup>15,19,24,25,30,35,39</sup>

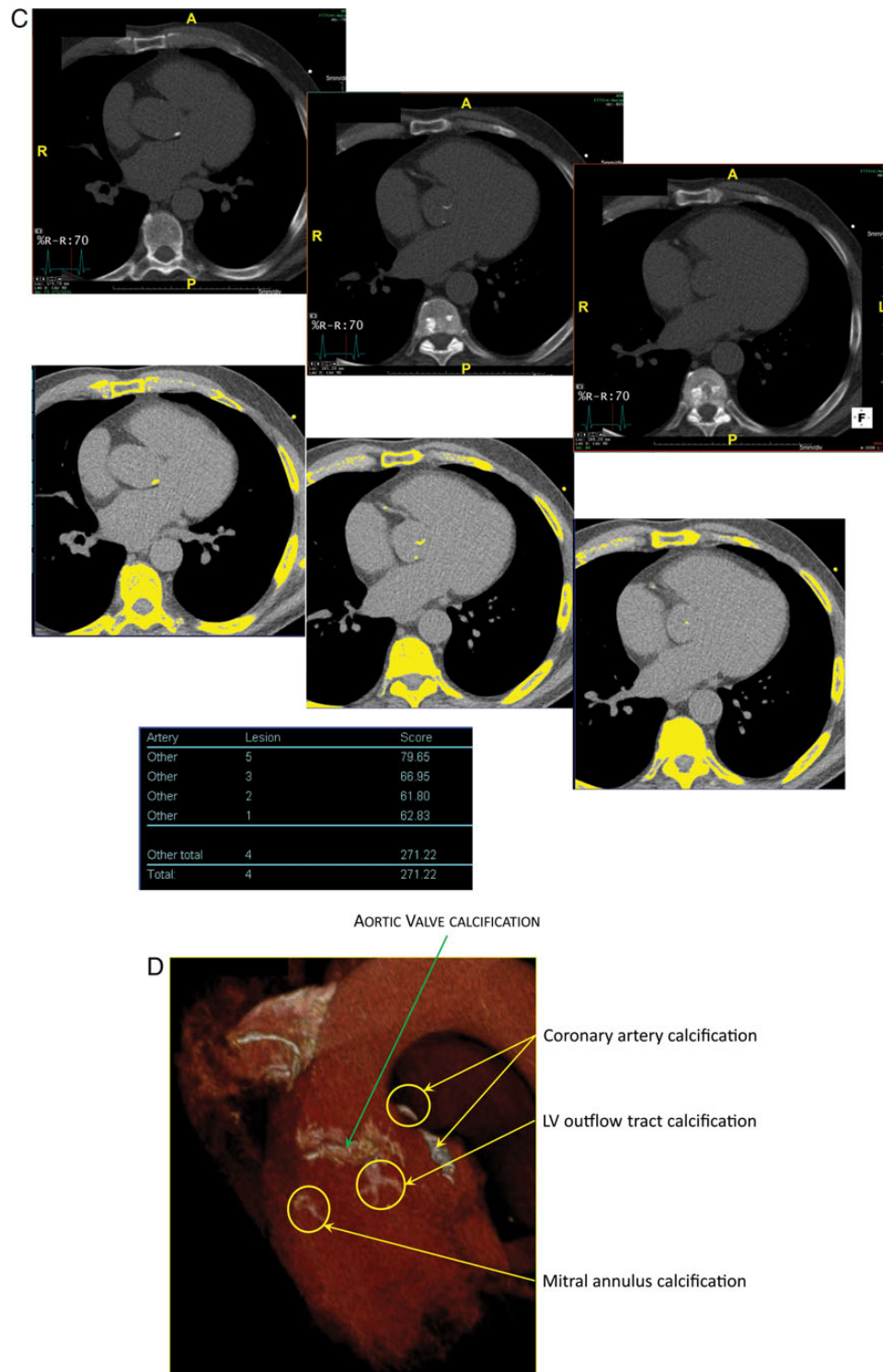
The surgical risk of patients with AS having an indication for AVR should be estimated using the integrative approach recommended in the guidelines and classified as: low, intermediate, high, and



**Figure 4** Quantitation of aortic valve calcium by multi-detector computed tomography for the assessment of stenosis severity in low-gradient aortic stenosis. (A) Multi-detector computed tomography can be used to quantitate aortic valve calcification by the modified Agatston method. With this method, calcification is defined as four adjacent pixels with density >130 Hounsfield units. Different cut-point values of valve calcium score should be used in women (>1200 AU) vs. men (>2000 AU) to differentiate true-severe vs. pseudo-severe stenosis in low-flow, low-gradient aortic stenosis. (B) Serial multi-detector computed tomography slices at the level of the aortic valve showing a severely calcified valve with a calcium score of 5040 AU consistent with true-severe aortic stenosis. Calcified areas are displayed in yellow in the bottom images. (C) Mild calcification (score 271 AU) consistent with pseudo-severe aortic stenosis. (D) Pitfalls in the assessment of aortic valve calcification by multi-detector computed tomography. For the calculation of calcium score, it is important to only include aortic valve calcification and exclude calcification of aorta, coronary arteries, LVOT, and mitral annulus. Abbreviations as in Figures 1 and 2.

prohibitive. Given that patients with classical LF-LG AS have, by definition, a reduced LVEF, their surgical risk is never low and ranges from intermediate to prohibitive depending on the other

co-morbidities. The approach proposed in the guidelines combines EuroSCORE or STS risk estimate, criteria of frailty, the presence of major organ system dysfunction, and procedure-specific



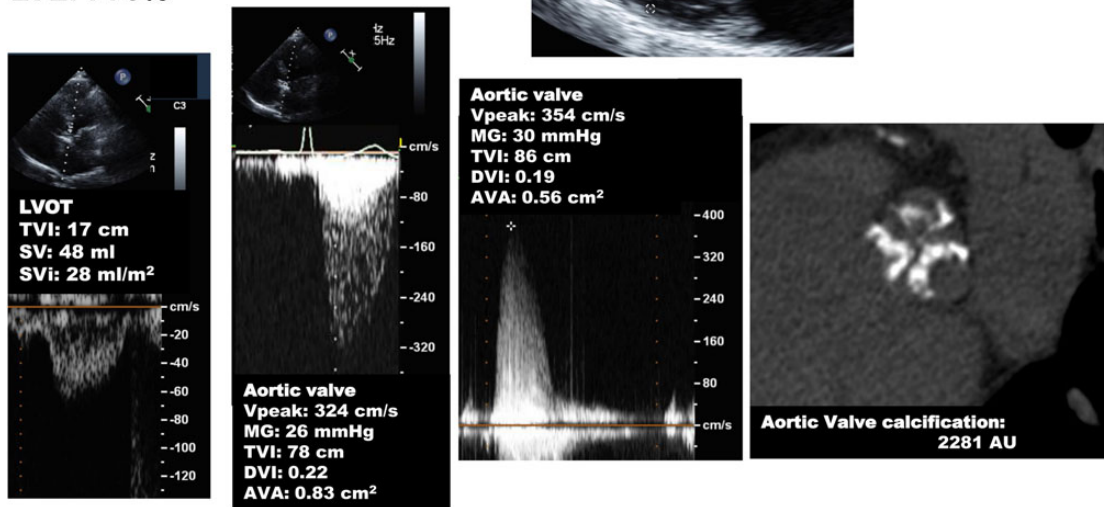
**Figure 4** Continued.

impediments. However, in the patients with LF-LG AS, the surgical risk stratification process should also integrate specific risk factors that are not included in the risk assessment algorithm proposed in the guidelines.<sup>1,2</sup> In particular, patients with very low

pre-operative gradient, the absence of flow reserve, markedly reduced global longitudinal strain should be considered at high surgical risk, even if the guidelines risk assessment suggests intermediate risk.

Woman – 78 y.o.  
 SBP: 145 mmHg DBP: 76 mmHg  
 BSA: 1.7 m<sup>2</sup>

Hypertension treated with ACEI  
 Hyperlipidemia  
 NYHA Class: III  
 LVEF: 70%



**Figure 5** Patient with paradoxical (preserved left ventricular ejection fraction) low-flow, low-gradient severe aortic stenosis. This case underlines the importance of multi-window continuous-wave Doppler interrogation for the measurement of the aortic velocity and gradient. In this patient, the gradient was higher at the right parasternal window than at the apical window. It is also important to rule-out error in the measurement of stroke volume. In this patient, the stroke volume measured by pulsed wave Doppler in the LVOT (48 mL) is corroborated by the stroke volume obtained with the modified Teichholz method: LV end-diastolic volume by Teichholz (70 mL)  $\times$  left ventricular ejection fraction by biplane Simpson (70%) = 49 mL. The patient is in low flow (SVI: 28 mL/m<sup>2</sup>). Aortic valve calcium score by multi-detector computed tomography corroborates presence of true-severe stenosis. ACEI, angiotensin conversion enzyme inhibitor; BSA, body surface area; DVI, Doppler velocity index; LVDd, LV end-diastolic diameter; IVS th, interventricular septum thickness; PWth, posterior wall thickness; SBP/DBP, systolic and diastolic blood pressure. Other abbreviations as in Figures 1, 2, and 3.

## Therapeutic management

Among patients with classical LF-LG AS, those with evidence of true-severe AS on DSE (i.e. progression Stage D2 in ACC-AHA guidelines) have a class IIa indication for AVR (Figure 2).<sup>1,2</sup> However, according to ESC-EACTS guidelines, the patients with no LV flow reserve on DSE have a weaker indication (IIb) for AVR because their stenosis severity often remains indeterminate with DSE and, in addition, they have a high operative risk with SAVR.<sup>1</sup> Despite the high surgical risk, these patients with no LV flow reserve nonetheless have much better survival with AVR compared with conservative management.<sup>19,24</sup> Furthermore, patients who survive operation have similar recovery of LV function and functional status and similar long-term survival compared with those with flow reserve.<sup>23</sup> Hence, AVR should be considered even in patients with no LV flow reserve or with other LF-LG-specific operative risk markers (e.g. severely reduced LVEF or global longitudinal strain) if the presence of severe AS is corroborated by the assessment of the projected AVA and/or of MDCT valve calcium score (Figures 2 and 3D–F). However, the

presence of these markers of high surgical risk may influence the selection of TAVR vs. SAVR.

Some studies suggest that TAVR may be associated with better and faster recovery of LV function and with improved survival compared with SAVR.<sup>41,42</sup> Furthermore, TAVR is associated with less prosthesis-patient mismatch,<sup>43–45</sup> which has been shown to be highly detrimental in patients with reduced LVEF including those with classical LF-LG AS.<sup>46–49</sup> The survival benefit of TAVR vs. SAVR may be more important in the subset of patients with no LV flow reserve. In the PARTNER-I Cohort B (inoperable patients) trial, TAVR was associated with a major survival benefit compared with conservative management in patients with classical LF-LG AS.<sup>50</sup> In the Cohort A (high surgical risk), survival was similar in the TAVR vs. SAVR arms.<sup>50</sup> However, patients with no LV flow reserve as well as those with very low LVEF were excluded from the PARTNER-I trial. Additional studies are necessary to confirm the potential superiority of TAVR over SAVR in patients with classical LF-LG severe AS (Stage D2). In the meantime, a comprehensive



assessment of surgical risk and post-AVR life expectancy should be performed by the Heart Team. In patients with expected life expectancy < 1 year, conservative therapy may be considered with the utilization of palliative balloon valvuloplasty for relief of cardiovascular symptoms and improvement of quality of life (Figure 2). In patients with classical LF-LG severe AS, prohibitive surgical risk, and life expectancy > 1 year, TAVR is recommended. In patients with high surgical risk, TAVR may be preferable to SAVR, whereas in those with intermediate risk, SAVR or TAVR may be considered depending on the evaluation by the Heart Team (Figure 2).

Coronary artery disease is frequent in patients with classical LF-LG AS and it contributes to the LV dysfunction, low-flow state, symptoms, and adverse cardiac events. Hence, percutaneous or surgical coronary revascularization should be considered whenever it is necessary.<sup>51</sup> This may be performed as a staged approach (percutaneous revascularization first and then AVR) or as a concomitant procedure at the time of surgical or transcatheter AVR.

Patients with pseudo-severe AS should, a priori, be managed conservatively (Figure 2).<sup>37</sup> However, they require optimized heart failure therapy, percutaneous coronary revascularization if indicated, and close echocardiographic and clinical follow-up. These patients may eventually necessitate AVR if the stenosis progresses during follow-up and/or if they do not improve despite optimized medical therapy. Given that even a moderate AS may be highly detrimental in the context of severely depressed LV function, it is possible that some patients with pseudo-severe AS and persistent heart failure symptoms despite optimal medical therapy may benefit from AVR. This provocative hypothesis would merit to be tested in a randomized trial.

Up to 70% of patients with classical low-flow AS have concomitant LV dyssynchrony,<sup>52</sup> which may contribute to the low LVEF, the LF-LG AS pattern, and to the lack of LV flow reserve on DSE. In these patients, cardiac resynchronization therapy has been shown to improve LV function and patient clinical status. Hence, in patients with classical LF-LG AS and LV dyssynchrony, cardiac resynchronization therapy should be considered first and the echocardiographic parameters, symptomatic status, and indication for AVR then be re-assessed.<sup>52,53</sup>

## Paradoxical (Preserved Left Ventricular Ejection Fraction) Low-Flow, Low-Gradient Aortic Stenosis

### Definition and pathophysiology

Paradoxical LF-LG AS is defined as an AVA < 1.0 cm<sup>2</sup>, indexed AVA < 0.6 cm<sup>2</sup>/m<sup>2</sup>, mean gradient < 40 mmHg, LVEF ≥ 50%, and presence of low flow (stroke volume index < 35 mL/m<sup>2</sup>) (Figures 1, 5, and 6).<sup>1,2</sup> Given that the transvalvular flow rate is not only dependent on stroke volume but also on LV ejection duration, some investigators proposed to define low flow as a mean transvalvular flow rate < 200 mL/s.<sup>54,55</sup>

An important proportion (25–35% depending on institution/country) of patients with AS and preserved LVEF have a low-flow state.<sup>3–5,8–10,17,36,50,56–58</sup> In these patients, the reduced stroke

volume is generally related to pronounced LV concentric remodeling with small LV cavity, impaired LV diastolic filling, and reduced LV systolic longitudinal function (Figure 5).<sup>3,6,11,32,58</sup> Paradoxical LF-LG AS does, in fact, share many pathophysiological and clinical similarities with preserved-LVEF heart failure.<sup>3,11,59</sup> Indeed, these entities are often associated with older age, female sex, and systemic hypertension. Furthermore, the mechanisms (impaired diastolic filling and systolic longitudinal function) underlying the reduction in stroke volume is similar in both entities.

Atrial fibrillation is also a frequent and important factor contributing to the decrease in LV outflow in AS patients with preserved LVEF.<sup>8</sup> Other factors may lead to a decrease in LV stroke volume and transvalvular flow rate including significant mitral regurgitation, mitral stenosis, tricuspid regurgitation, or right ventricular dysfunction (Figure 6).<sup>8,60</sup> Hence, a large proportion of patients with AS have a low-flow state despite a preserved LVEF and these patients have worse outcomes.<sup>3,36,50,61,62</sup> Furthermore, because of the low-flow state, patients often have a low-gradient AS despite a small AVA (Figure 1), which makes difficult the assessment of stenosis severity. The measurement of stroke volume index should therefore be systematically integrated in the Doppler-echocardiographic evaluation of the AS patient and the presence of low flow, i.e. stroke volume index < 35 mL/m<sup>2</sup>, should be reported.<sup>1,2</sup>

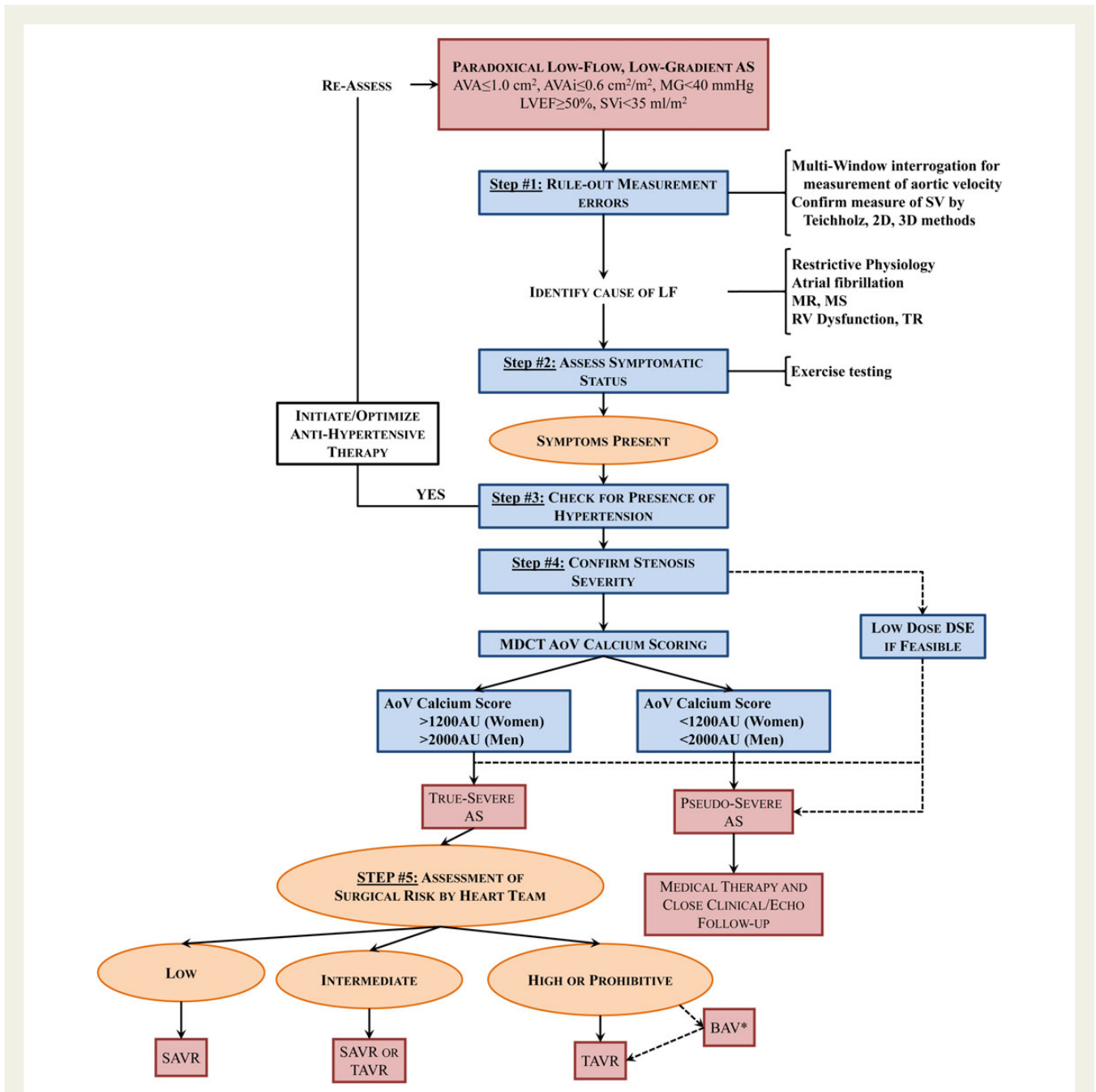
### Stenosis severity

If the echocardiographic exam reveals the presence of a low-flow state, one should identify the underlying cause of the reduced stroke volume (Figure 6). If no obvious factor can be identified to explain the low flow, one should then re-assess the accuracy of the echocardiographic measure of stroke volume and/or consider other modalities to measure flow.

The Doppler velocity index (ratio of LVOT to aortic velocity–time integrals) may also be used to corroborate the accuracy of AVA measurements and enhance prognostication in patients with LG AS.<sup>63,64</sup> The finding of a small AVA with a Doppler velocity index > 0.25 should raise the possibility of LVOT diameter or velocity underestimation. A hybrid method where LVOT area is measured by MDCT and flow velocities by Doppler-echocardiography has also been proposed to calculate the AVA and grade AS severity.<sup>65,66</sup> However, given that the values of AVA obtained with this hybrid method are systematically larger than those obtained by echocardiography, one cannot directly apply the same cut-point value (i.e. < 1.0 cm<sup>2</sup>) to define severe AS. In this regard, a recent study reported that the hybrid AVA does not improve the correlation with the transvalvular gradient or the prediction of mortality compared with the echocardiographic AVA.<sup>65</sup> Moreover, the best cut-point value to predict outcomes was close to 1.0 cm<sup>2</sup> for the echocardiographic AVA (which is consistent with the guidelines criteria) but it was larger for the hybrid AVA: 1.2 cm<sup>2</sup>.

A small AVA may in fact correspond to a moderate AS and thus a low gradient in a patient with a small body size. Hence, in patients with paradoxical LF-LG AS and small body size, it is important to calculate the indexed AVA and a value > 0.6 cm<sup>2</sup>/m<sup>2</sup> would indicate a moderate AS.<sup>2</sup> On the other hand, the indexed AVA may overestimate the stenosis severity in obese patients.

Once the presence of bona fide paradoxical LF-LG AS is confirmed, it is then important to differentiate true- vs. pseudo-severe



**Figure 6** Algorithm for the management of paradoxical (preserved left ventricular ejection fraction) low-flow, low-gradient aortic stenosis. AVAi, indexed aortic valve area; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation; other abbreviations as in Figures 1, 2, and 3.

AS (Figure 6). Some studies suggest that DSE may be used for this purpose in patients with paradoxical LF-LG AS.<sup>67</sup> A low-dose protocol (up to 20  $\mu\text{g}/\text{kg}/\text{min}$ ) starting at 2.5  $\mu\text{g}/\text{kg}/\text{min}$  with careful monitoring of ECG, blood pressure, and LVOT velocity should be used in these patients. The same DSE parameters and criteria described for classical LF-LG AS can be applied to paradoxical LF-LG AS in order to identify true-severe stenosis. Approximately, one-third of patients with paradoxical LF-LG AS has pseudo-severe AS, which is similar to that observed in classical LF-LG AS.<sup>67</sup> Dobutamine stress echocardiography should not be performed

in patients with restrictive LV physiology pattern, which is frequently found in the paradoxical LF-LG AS population. Exercise-stress echocardiography may be useful in patients with paradoxical LF-LG who claim to be asymptomatic or have equivocal symptoms to: (i) ascertain the symptomatic status and (ii) to differentiate true- vs. pseudo-severe AS.<sup>67</sup> Hence, the preferred approach to corroborate stenosis severity in these patients is rather to assess the morphology of the valve and the degree of aortic valve calcification by echocardiography and/or MDCT (Figures 4 and 5). The same cut-points of aortic calcium score

and density used for classical LF-LG AS can be applied to paradoxical LF-LG AS.<sup>27</sup>

## Outcomes and risk stratification

Patients with paradoxical LF-LG AS generally have worse outcomes compared with moderate AS, high-gradient AS, and NF-LG AS but better outcomes compared with classical LF-LG AS.<sup>3,5,8–10,56,58,68,69</sup> Given the higher proportion of women, the older age, the higher prevalence of hypertension, restrictive LV physiology, atrial fibrillation, low LV outflow, and small aortic annulus/root, these patients are at higher surgical risk compared with those with high-gradient AS.<sup>9,17,36,50,62,70,71</sup> However, several studies reported that, in patients with paradoxical LF-LG AS, survival is markedly improved by AVR compared with conservative management.<sup>8,50,56,57,69,72,73</sup> Except the randomized PARTNER I cohort B trial that reports better survival after TAVR compared with conservative management in paradoxical LF-LG patients,<sup>50</sup> all studies that evaluate survival in paradoxical LF-LG patients according to type of treatment were observational and residual confounding factors cannot be excluded. Nevertheless, a recent meta-analysis reported that (i) patients with paradoxical LF-LG AS have 67% higher risk of mortality compared with high-gradient AS and (ii) AVR reduces mortality by 57% in patients with paradoxical LF-LG AS.<sup>69</sup>

More advanced LV myocardial impairment as documented by higher degree of myocardial fibrosis measured by cardiac resonance imaging, moderate/severe LV diastolic dysfunction, reduced global LV systolic longitudinal strain, and very low stroke volume index are associated with increased risk of mortality in patients with paradoxical LF-LG AS and with worse outcomes following AVR.<sup>32,36,58,70,74</sup> In some studies, basal longitudinal strain has been shown to be more sensitive than global longitudinal strain to predict outcomes.<sup>6,75</sup> However, regional strain is more susceptible to measurement variability compared with global strain.

Although plasma levels of BNP have been shown to be useful for risk stratification in patients with classical LF-LG AS,<sup>38</sup> their role is unclear for those with paradoxical LF-LG AS.<sup>5,76,77</sup> In contrast to patients with classical LF-LG AS, those with paradoxical LF-LG AS have pronounced LV concentric remodelling and small LV cavities. The extent of myocardial stretch and ensuing release of natriuretic peptides may thus not accurately reflect the severity of impairment of myocardial structure/function in these patients.

## Therapeutic management

Aortic valve replacement should be considered in symptomatic patients with bona fide paradoxical LF-LG and true-severe AS (Stage D3 in the ACC/AHA guidelines) confirmed by echocardiography, DSE, and/or MDCT (Figures 5 and 6).<sup>1,2</sup> Given that systemic arterial hypertension is frequent in these patients and may contribute to the LF-LG pattern as well as to the symptoms and cardiac events, it is first important to institute/optimize anti-hypertensive therapy if hypertension is present and then reassess the echocardiographic parameters, symptoms, and indication of AVR once blood pressure is normalized (Figure 6).<sup>2,3,78,79</sup> Patient with paradoxical LF-LG AS and pseudo-severe AS should be managed conservatively with optimization of anti-hypertensive therapy (Figure 6).

Recent studies suggest that TAVR may be superior to SAVR in the subset of patients with paradoxical LF-LG AS.<sup>50</sup> Indeed, these

patients have some features (restrictive LV physiology, small aortic annulus/root) that may substantially increase the risk of perioperative morbidity/mortality as well as that of prosthesis-patient mismatch with SAVR.<sup>17,80</sup> The combination of paradoxical LF-LG AS and prosthesis-patient mismatch is associated with markedly increased risk of mortality following SAVR.<sup>80</sup> In the PARTNER-I Cohort A trial, TAVR was associated with better 1-year survival compared with SAVR in patients with paradoxical LF-LG AS.<sup>50</sup> Further studies are necessary to confirm the potential superiority of TAVR vs. SAVR in this subset of patients. In the meantime, TAVR may be preferable to SAVR in patients with paradoxical LF-LG AS, particularly if they are considered at high surgical risk (Figure 6). In patients in whom it is uncertain that the symptoms are solely related to AS and/or will improve following AVR, a staged approach with balloon valvuloplasty first and then TAVR 6 months later if symptoms improve may be considered (Figures 2 and 6).

## Normal-Flow, Low-Gradient Aortic Stenosis

### Definition and pathophysiology

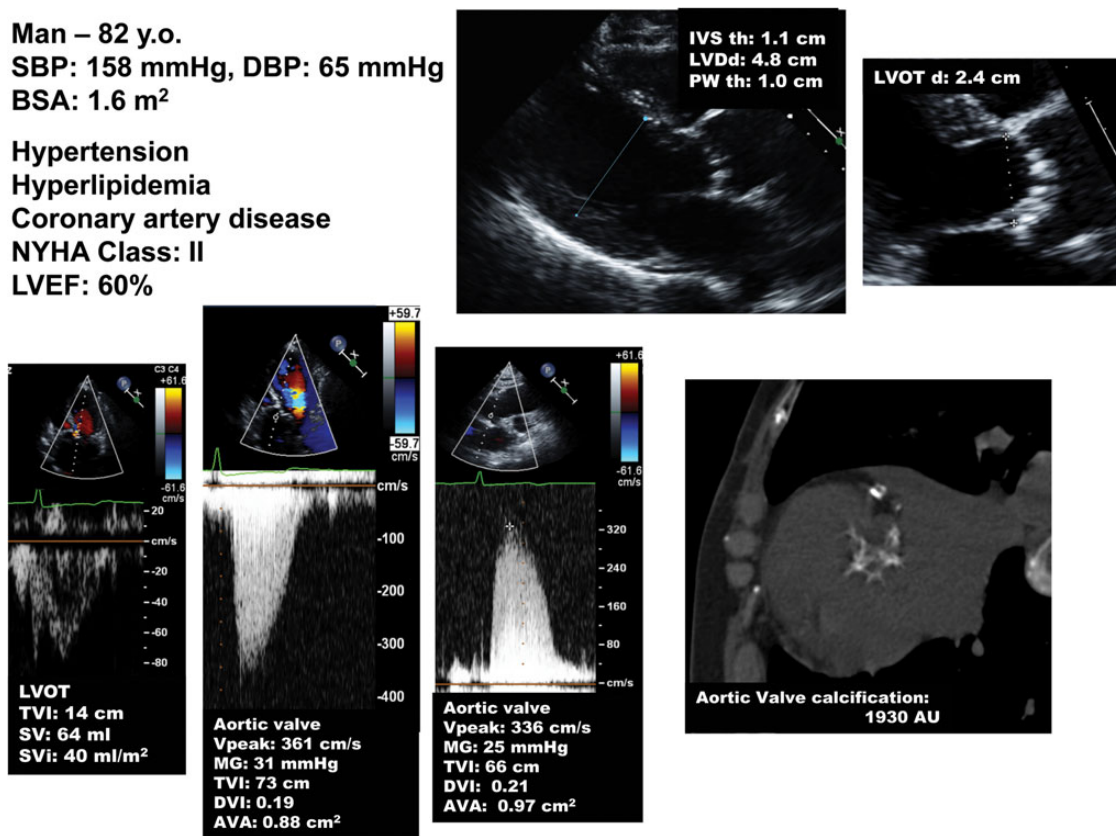
Normal-flow, LG AS is defined as an AVA  $< 1.0 \text{ cm}^2$ , indexed AVA  $< 0.6 \text{ cm}^2/\text{m}^2$ , mean gradient  $< 40 \text{ mmHg}$ , LVEF  $\geq 50\%$ , but normal flow, i.e. stroke volume index  $> 35 \text{ mL}/\text{m}^2$  (Figures 1 and 7). This entity is relatively frequent (15–40%) and may be related to inherent discrepancies in the guidelines criteria for severe AS.<sup>4,5,10,11,56,58</sup> From a haemodynamic stand-point, the AVA cut-point value of  $1.0 \text{ cm}^2$ , as proposed in the guideline to define severe AS, does not correspond to a mean gradient of 40 mmHg but rather to a gradient of 30–35 mmHg.<sup>4</sup> To reconcile this inherent discrepancy, some investigators suggested lowering the severity cut-point value of AVA from  $1.0$  to  $0.8 \text{ cm}^2$ .<sup>4,81</sup> However, several studies showed that the optimal cut-point value of AVA to predict mortality is  $1.0 \text{ cm}^2$ , whereas the one for the gradient is 30 mmHg.<sup>82–84</sup> Hence, it seems preferable to maintain the status quo with regards to the cut-point values of AVA and gradient and use the AVA cut-point ( $1.0 \text{ cm}^2$ ) as a sensitive marker of severe AS and the gradient cut-point (40 mmHg) as a specific marker. Some studies also suggest that reduced aortic compliance and associated systolic hypertension may lead to a substantial decrease in gradient and thus to a NF-LG pattern in patients with severe AS (Figure 7).<sup>78,85,86</sup>

### Outcomes and risk stratification

In patients with LG AS, lower stroke volume index is a powerful predictor of outcomes both before and after AVR.<sup>17,36,50,61,74,87</sup> Patients with NF-LG AS are generally at a less advanced stage of the disease and they have better survival compared with paradoxical LF-LG or high-gradient AS.<sup>5,58,69</sup> Accordingly, a recent study found no difference in survival between patients with NF-LG AS treated by early surgery vs. by conservative management with wait-for-symptoms strategy.<sup>88</sup> On the other hand, other studies, including a recent meta-analysis, revealed that AVR may improve survival in these patients.<sup>9,56,69,72</sup> These findings may be explained by the fact that this subset of patients is highly heterogeneous and that a substantial proportion (40–50%) of these patients may nonetheless

Man – 82 y.o.  
 SBP: 158 mmHg, DBP: 65 mmHg  
 BSA: 1.6 m<sup>2</sup>

Hypertension  
 Hyperlipidemia  
 Coronary artery disease  
 NYHA Class: II  
 LVEF: 60%



**Figure 7** Patient with normal-flow, low-gradient aortic stenosis. This patient has a normal flow (stroke volume index  $> 35 \text{ mL/m}^2$ ), small aortic valve area, small indexed aortic valve area, and low mean transvalvular gradient at echocardiography. As in the patient with paradoxical low-flow, low-gradient (Figure 5), it is important first to rule-out measurement errors and then confirm stenosis severity, especially if the patient is symptomatic. In this patient, aortic valve calcium score by multi-detector computed tomography suggests the presence of a moderate to severe aortic stenosis.

have severe stenosis.<sup>27</sup> Hence, it is important to perform additional tests to confirm stenosis severity in patients with NF-LG AS who are symptomatic.

### Stenosis severity

As in patients with paradoxical LF-LG AS, the first step is to rule-out measurement errors (Figure 6). Given that the flow rate is already normal in patients with NF-LG AS, DSE has limited utility in these patients, and aortic valve calcium scoring by MDCT is likely the preferred approach to differentiate severe from non-severe AS.<sup>27</sup>

### Therapeutic management

There is no specific definition and recommendation in the guidelines for the patients with NF-LG AS. A similar algorithm as the one proposed for paradoxical LF-LG AS (Figure 6) may be applied for NF-LG AS and should include the following steps: Step #1: Rule-out measurement errors, Step #2: Assess symptomatic status; Step #3: Check for presence of hypertension, and, if any, institute/optimize anti-hypertensive therapy and re-assess parameters of stenosis severity and symptomatic status; Step #4: Confirm stenosis severity; Step #5: If stenosis is severe and AVR is indicated; assess surgical

risk to select the type of AVR: SAVR vs. TAVR. Patients with NF-LG AS who have no symptoms or no evidence of severe AS should be treated conservatively. In light of the results of some recent studies,<sup>69</sup> AVR should probably be considered in symptomatic patients with NF-LG AS in whom MDCT or other imaging modalities support the presence of severe AS. However, further studies are needed to confirm the benefit of AVR in symptomatic patients with NF-LG severe AS.

### Conclusion

Low-gradient AS is one of the most challenging entities in valvular heart disease. It includes three main subtypes: (i) classical (reduced LVEF) LF-LG, (ii) paradoxical (preserved LVEF) LF-LG, and (iii) NF-LG AS. One of the most important clinical challenges in these patients with LG AS is to differentiate a true-severe AS that generally benefits from AVR vs. a pseudo-severe AS that should be managed conservatively. A low-dose DSE may be used for this purpose in patients with classical LF-LG AS, whereas aortic calcium scoring by MDCT is the preferred modality in those with paradoxical LF-LG or NF-LG AS. Although patients with LF-LG severe AS have worse

outcomes than those with high-gradient AS following AVR, they nonetheless get an important survival benefit with this intervention. Some studies suggest that TAVR may be superior to SAVR in patients with LF-LG AS, and particularly in those with classical LF-LG AS and no LV flow reserve or those with paradoxical LF-LG AS.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Authors' contributions

P.P. handled funding and supervision; M.A.C. and P.P. drafted the manuscript; M.A.C., J.M., P.P.: made critical revision of the manuscript for key intellectual content.

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