

EDITORIAL COMMENT

Discordant Low-Gradient Aortic Stenosis With Preserved Left Ventricular Ejection Fraction



Setting the Record Straight*

Philippe Pibarot, DVM, PhD, Marie-Annick Clavel, DVM, PhD

Low-gradient (LG) aortic stenosis (AS) is one of the most challenging valvular heart disease entities.^{1,2} The main diagnostic challenge posed by LG-AS is that these patients present with discordant grading at transthoracic echocardiography with an aortic valve area (AVA) and indexed AVA being in the severe range (<1.0 cm² and <0.6 cm²/m², respectively) but a peak aortic jet velocity and mean transvalvular pressure gradient being non-severe (<4 m/s and <40 mmHg, respectively). This situation raises uncertainty about the true severity of the stenosis and thus about the indication of aortic valve replacement (AVR) if the patient is symptomatic and/or has reduced left ventricular (LV) ejection fraction (LVEF <50%). Previous studies and both the American³ and European guidelines⁴ have identified 3 categories or patterns of LG-AS: 1) Classical low-flow, LG-AS characterized by a LVEF <50% and generally a low-flow state defined as a stroke volume index <35 ml/m²; 2) Paradoxical low-flow, LG-AS characterized by a preserved LVEF (≥50%) but nevertheless a low-flow state; 3) Normal-flow LG-AS with preserved LVEF and normal flow on the basis of stroke volume index (≥35 ml/m²).

In the multicenter study published in this issue of *JACC: Advances*, De Azevedo et al⁵ analyzed the

outcomes of patients with discordant low-gradient severe AS (DLG-SAS), ie, patients with LG-AS and preserved LVEF, regardless of their flow status: low or normal. So, this DLG-SAS group included both patients with paradoxical low-flow LG-AS and those with normal-flow LG-AS. They then compared the outcome of the patients with DLG-SAS vs those with moderate AS (MAS) and those with high-gradient severe AS (HG-SAS). This analysis was conducted in the whole cohort that included 2,582 patients and in the subset of unoperated patients (n = 1,812). The main findings of this study⁵ are the following: 1) The survival of the DLG-SAS group was intermediate between MAS and HG-SAS: ie, worse than MAS but better than HG-SAS. 2) As expected, at comparable mean gradient, the lower the AVA and indexed AVA, the worse the prognosis, and vice versa, at comparable indexed AVA, the higher the gradient, the worse the prognosis. In light of these findings, the authors concluded that DLG-SAS is an intermediate form of the aortic valve disease continuum. The authors should be commended for conducting this multicenter study in a large series of patients with DLG-AS and preserved LVEF. This study confirms and expands the knowledge on risk stratification of this challenging entity of DLG-SAS with preserved LVEF. There are, however, several limitations in this study, which merit to be highlighted and discussed.

FLOW MATTERS IN LOW-GRADIENT AORTIC STENOSIS WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

In both the European and American guidelines,^{3,4} there is a clear distinction between paradoxical (ie, preserved LVEF) low-flow LG-AS and normal-flow LG-AS. The reason for this distinction is that these

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

From the Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart & Lung Institute, Laval University, Québec, Canada.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

2 entities have different implications in terms of prognosis and therapeutic management. For the first group, paradoxical low-flow LG-AS, there is, indeed, a Class I (American guidelines) or IIa (European guidelines) indication of AVR if AS severity is confirmed to be severe, whereas for the second group, normal-flow LG-AS, the European guidelines state that AS is unlikely to be severe and do not provide any recommendation for AVR and the American guidelines do not even mention or address this subset of patients. Several studies and meta-analyses have reported that low-flow state is a marker of worse prognosis and that patients with paradoxical low-flow, LG-AS have therefore reduced survival compared to those with normal-flow LG-AS.⁶⁻¹⁰ Furthermore, the proportion of patients with true-severe AS is, as expected, much higher in paradoxical low-flow than in normal-flow LG-AS. These studies also reported that LG-AS patients with evidence of true-severe stenosis benefit of AVR, regardless of their flow status: normal or low.⁶⁻¹⁰ Given that in most analyses conducted in the present study, all patients with LG-AS and preserved LVEF were pooled together into the same group (DLG-SAS), this study does not allow answering to the key question of what is the prognosis of paradoxical low-flow vs normal-flow LG-AS as identified and distinguished in the guidelines and how we should risk stratify and treat these 2 different subtypes of LG-AS. In the online supplement, the authors, however, present the comparison of the outcomes of DLG-SAS with low-flow (ie, paradoxical low-flow LG-AS) vs those with normal flow (ie, normal-flow, LG-AS). It is somewhat surprising to see that there was only a trend for higher mortality in low-flow DLG-SAS group vs normal-flow DLG-SAS. Numerous studies and meta-analyses indeed reported that as expected, low-flow state is a powerful marker of worse prognosis in AS and other valvular heart diseases.^{6,11} It would also had been interesting to compare these 2 subgroups of LG-AS (paradoxical low-flow and normal-flow LG-AS, as described in the guidelines, vs MAS and HG-SAS groups).

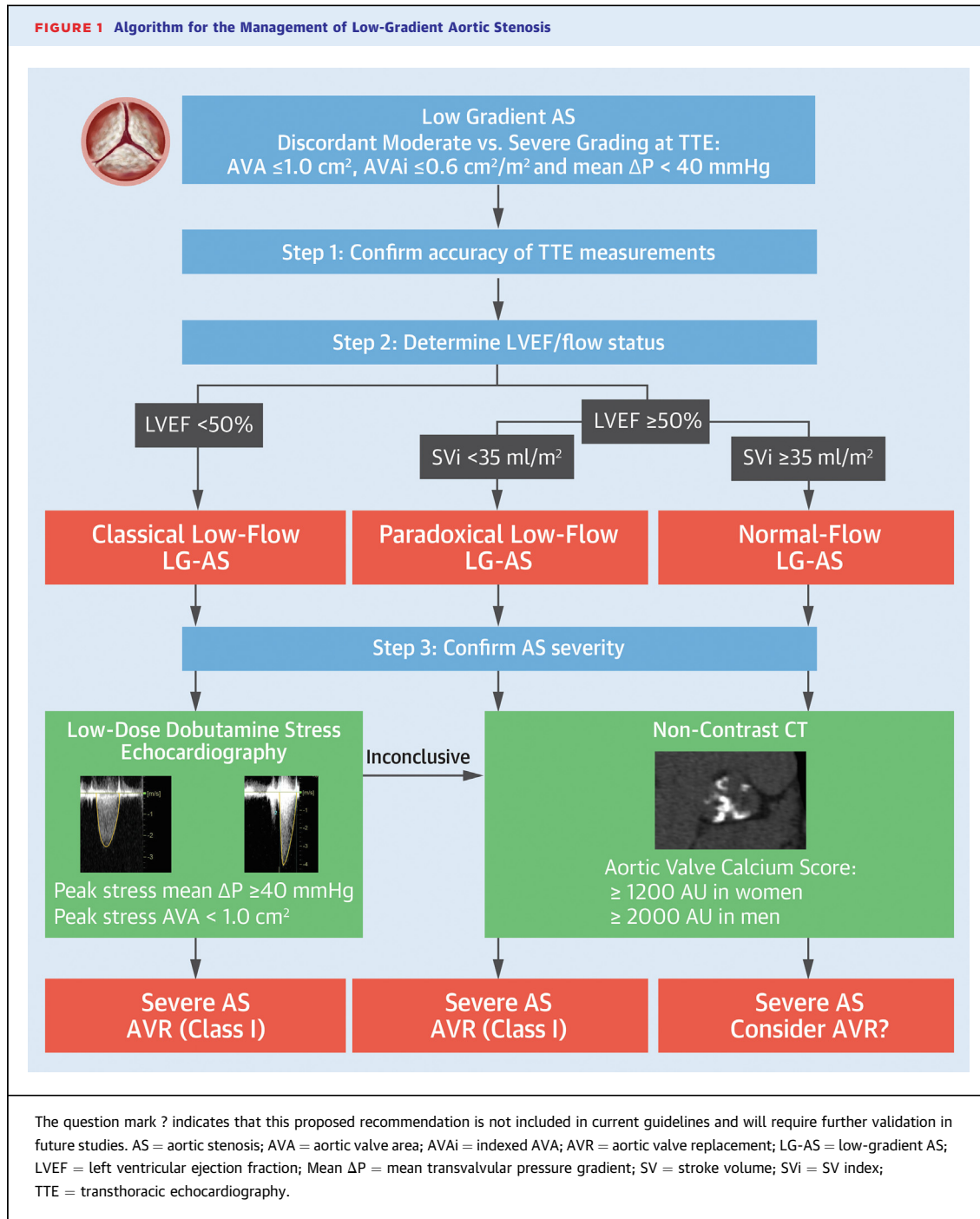
CONFIRMATION OF STENOSIS SEVERITY IS KEY IN LOW-GRADIENT AORTIC STENOSIS

One major issue with regard to the terminology and classification used by the authors to describe the

study group is the label: 'DLG severe' AS (DLG-SAS), which, de facto, implies that all patients in this group have severe AS. However, it is likely that a large proportion of these patients with DLG-SAS, in fact, had pseudo-severe, that is, non-severe AS. Both the American and European guidelines recommend performing non-contrast computed tomography (CT) to quantitate aortic valve calcification and therefore differentiate true-severe vs non-severe AS, particularly in patients with paradoxical low-flow, LG-AS.^{3,4} The adjudication of AS severity is extremely important in patients with LG-AS, regardless of LVEF (low or preserved) or flow (low or normal), because 30 to 50% of these patients actually have "pseudo-severe" AS and thus no indication for AVR. In the present study, there was no confirmation of the actual AS severity and the authors pooled together patients with true-severe and those with pseudo-severe AS. It is thus not surprising that this pooled subset of patients, which includes probably 60% severe and 40% moderate AS, displays a prognosis that is intermediate between HG-SAS patients (100% severe) and those with concordant moderate AS (100% moderate). The important question, which remained unanswered in this study, is thus: what is the prognosis of true-severe LG-AS vs HG-SAS and MAS, especially when treated conservatively. It is likely that the true-severe LG-AS group would have a prognosis similar or worse than those with HG-SAS, whereas those with non-severe LG-AS would have a prognosis similar to the MAS group.

ALGORITHM FOR THE MANAGEMENT OF LOW-GRADIENT AORTIC STENOSIS

In light of the data published in the literature, including in the present study, and of the recommendations presented in the guidelines, we would like to propose the following algorithm for the management of LG-AS (**Figure 1**): Step 1: Confirm the accuracy of the transthoracic echocardiography measurements of LVEF, stroke volume, AVA, and gradient. Step 2: Determine the LVEF/flow status: 1) Classical low-flow, LG-AS with reduced LVEF; 2) Paradoxical low-flow, LG-AS with preserved LVEF; 3) Normal-flow, LG-AS. Step 3: Confirm the actual AS severity using low-dose dobutamine stress echocardiography in patients with reduced LVEF and CT aortic valve calcium scoring in those with preserved



LVEF. Although severe AS is less likely in normal-flow than in low-flow LG-AS, it is reasonable to perform CT and eventually consider AVR in symptomatic patients with bona fide normal-flow LG-AS with severe aortic valve calcium score ($\geq 1,200$ AU in women and $\geq 2,000$ AU in men) (Figure 1).

In summary, the authors lumped together in a single heterogeneous group of patients labeled DLG-SAS, several subsets of patients (ie, paradoxical low-flow LG-AS, normal-flow LG-AS, pseudo-severe LG-AS, and true-severe LG-AS), which have different distribution of moderate vs severe AS severity and

different outcomes. Hence, the finding that the outcome of the DLG-SAS group is intermediate between HG-SAS and MAS is not surprising and is expected. On the other hand, this study does not allow identifying which subset of patients, within this heterogeneous group of patients, is at higher risk of adverse outcomes and should be referred to AVR. The results of the present study underlines the importance of going beyond the AVA, gradient and LVEF in patients with LG-AS and of considering additional important factors such as flow status and stenosis severity (Figure 1), when assessing the risk of adverse outcomes and determining the optimal timing and type of treatment in patient with LG-AS. Hence, further studies are now needed to determine what is the outcome and impact of AVR in patients with LG-AS and preserved LVEF, according to flow (low vs normal) and confirmed AS severity (true-severe vs non-severe).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Pibarot has received institutional funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Success for echocardiography core laboratory analyses and research studies in the field of interventional and pharmacologic treatment of valvular heart diseases, for which he received no personal compensation. Dr Clavel has received institutional funding from Edwards Lifesciences and Medtronic for CT core laboratory analyses and research studies in the field of interventional and pharmacologic treatment of valvular heart diseases. Dr Pibarot holds the Canada research Chair on valvular Heart Diseases and Dr Clavel the Canada Research Chair in Women Valvular Health, which are both funded by Canadian Institutes of Health Research.

ADDRESS FOR CORRESPONDENCE: Dr Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy #A2075, Québec, Québec G1V-4G5, Canada. E-mail: Philippe.Pibarot@med.ulaval.ca. Twitter: @ppibarot, @ClavelLabo.

REFERENCES

- Delgado V, Clavel MA, Hahn RT, et al. How do we reconcile echocardiography, computed tomography, and hybrid imaging in assessing discordant grading of aortic stenosis severity? *J Am Coll Cardiol Img*. 2019;12:267-282.
- Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J*. 2016;37:2645-2657.
- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450-500.
- Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561-632.
- De Azevedo D, Tribouilloy C, Maréchaux S, et al. Prognostic implications of discordant low-gradient severe aortic stenosis: comprehensive analysis of a large multicenter registry. *JACC Adv*. 2023;2(2):100254.
- Dayan V, Vignolo G, Magne J, Clavel MA, Mohty D, Pibarot P. Outcome and impact of aortic valve replacement in patients with preserved LV ejection fraction and low gradient aortic stenosis: a meta-analysis. *J Am Coll Cardiol*. 2015;66:2594-2603.
- Vinco G, Bergamini C, Pighi M, Golia G, Vassanelli C, Biancari F. Meta-analysis of the outcome of patients with low gradient severe aortic stenosis and preserved left ventricular ejection fraction. *Int J Cardiol*. 2013;168:5076-5078.
- Taniguchi T, Morimoto T, Shiomi H, et al. High-versus low-gradient severe aortic stenosis: demographics, clinical outcomes, and effects of the initial aortic valve replacement strategy on long-term prognosis. *Circ Cardiovasc Interv*. 2017;10:e004796.
- Salaun E, Clavel MA, Hahn RT, et al. Outcome of flow-gradient patterns of aortic stenosis after aortic valve replacement: an analysis of the PARTNER 2 trial and registry. *Circ Cardiovasc Interv*. 2020;13:e008792.
- Annabi MS, Côté N, Dahou A, et al. Comparison of early surgical or transcatheter aortic valve replacement versus conservative management in low-flow, low-gradient aortic stenosis using inverse probability of treatment weighting: results from the TOPAS prospective observational cohort study. *J Am Heart Assoc*. 2020;9:e017870.
- Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low flow, low gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856-2864.

KEYWORDS aortic stenosis, aortic valve replacement, echocardiography, low flow