JACC: CARDIOVASCULAR IMAGING VOL. 17, NO. 8, 2024

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Adjudication of Low-Flow, Low-Gradient Aortic Stenosis Severity

Dobutamine Stress Echocardiography and MSCT Are Complementary, Not Competitive

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

The adjudication of stenosis severity is the cornerstone of management of patients with aortic stenosis (AS), as aortic valve replacement is indicated only in patients with confirmed severe AS, except if the patient undergoes another cardiac intervention.[1] Rest transthoracic echocardiography (TTE) allows the confirmation of AS severity in 70% of patients. In such cases, the echocardiographic parameters of AS severity (aortic valve area [AVA], peak aortic jet velocity [V_{peak}], and mean gradient [MG]) are concordant (ie, AVA >1 cm^2 and MG <40 mm Hg or V_{peak} <4 m/s confirm moderate AS, and AVA ≤ 1 cm^2 and MG ≥ 40 mm Hg or V_{peak} ≥ 4 m/s confirm severe AS).

Unfortunately, in up to 30% of patients, echocardiographic markers of AS severity are discordant, and AS severity remains unknown on rest TTE. This discordant grading situation is generally the consequence of a low-flow state (stroke volume index <35 mL/m^2), where MG and V_{peak} may underestimate AS severity and AVA may overestimate AS severity. When a low-flow state is associated with reduced left ventricular ejection fraction (LVEF) (classical low-flow, low-gradient AS), low-dose dobutamine stress echocardiography (DSE) is suggested in the guidelines to differentiate truly severe from pseudosevere AS and confirm the indication for AVR. In patients with a low-flow state associated with preserved LVEF, the guidelines instead recommend adjudicating AS severity using the aortic valve calcium (AVC) score, measured using noncontrast electrocardiographically gated multislice computed tomography (MSCT). AVC has been shown to have a good correlation with hemodynamic severity of AS and to provide excellent discrimination between severe and nonsevere AS in patients with concordant grading on TTE.[2] However, the diagnostic accuracy of AVC had never been tested specifically in patients with a low-flow state and ensuing discordant grading.

In a study reported in this issue of *JACC: Cardiovascular Imaging*, Adrichem et al[3] assessed the diagnostic value of MSCT-derived AVC compared with DSE in the context of a multicenter observational cohort study including 219 patients with low-flow, low-gradient AS (mean age 78 years, 75% men) prior to transcatheter aortic valve replacement. The cohort was composed predominantly (92%) of patients with classical (ie, reduced LVEF) low-flow, low-gradient AS.

The sensitivity, specificity, and positive and negative predictive values of AVC for the identification of truly severe AS were 44.3%, 56.5%, 50.0%, and 50.8%, respectively. The area under the receiver-operating characteristic curve was 0.51 for men and 0.52 for women. The investigators conclude that MSCT-derived AVC scores show poor discrimination between grades of AS severity by DSE and cannot replace DSE in the diagnostic work-up of low-flow, low-gradient AS.

The investigators should be commended for conducting this real-life study that further highlights the challenges cardiologists face in the adjudication of AS severity in patients with low-flow, low-gradient AS. Obviously, this study suggests that AVC is not a panacea for confirming AS severity in this context and that none of the methods that are used for this purpose (ie, TTE, DSE, and MSCT) is optimal and can be

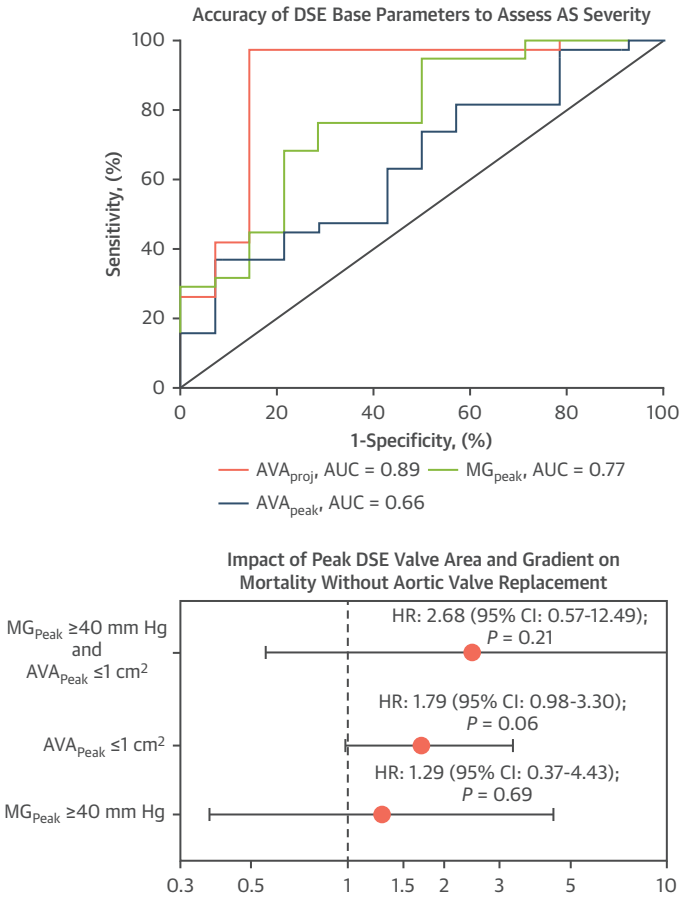
From the Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart and Lung Institute, Laval University, Québec, Québec, Canada.

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.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2024.04.018

JACC: CARDIOVASCULAR IMAGING, VOL. 17, NO. 8, 2024
AUGUST 2024:861–864

FIGURE 1 Accuracy of DSE Parameters to Assess AS Severity and Impact on Outcomes in Patients With Low-Flow, Low-Gradient AS Treated Medically



The top panel shows the receiver-operating characteristic curves of peak dobutamine stress echocardiographic (DSE) aortic valve area (AVA_{peak}), peak DSE mean gradient (MG_{peak}), and projected AVA at normal flow rate (AVA_{proj}) to predict severe aortic stenosis (AS). The bottom panel shows the HR and 95% CI of the different DSE criteria to predict mortality under medical management (n = 88). Analyses are adjusted for age, sex, functional capacity (Duke activity status index), kidney failure, and DSE left ventricular ejection fraction. The data presented in these figures are from Annabi et al.[9]

used in isolation to adjudicate AS severity. However, the present study has several major limitations that should be discussed.

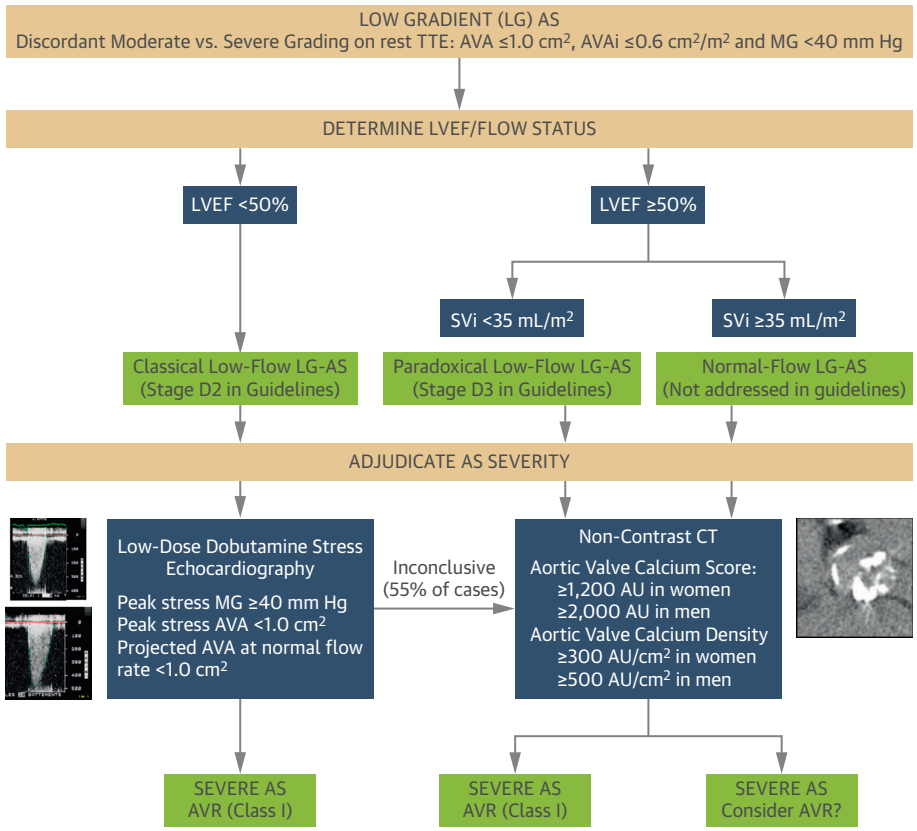
Among the patients enrolled in this study, 32 (15%) underwent only contrast-enhanced MSCT, which has been shown to substantially underestimate AVC compared with noncontrast MSCT.[4,5] Hence, AS severity may have been underestimated in these patients, and this may have dampened the sensitivity and positive predictive value of AVC in this study. Also, the investigators used only absolute AVC score to adjudicate AS severity. Previous studies have reported that AVC density (ie, AVC score divided by aortic annular area) is superior to AVC to assess stenosis severity and predict outcomes.[6,7]

Multiple studies have shown a strong association between severe AVC and mortality or need for aortic valve replacement,[2,8] and AVC has been adopted in the guidelines to confirm AS severity in patients with low-flow, low-gradient AS, particularly those with preserved LVEF.[1] In the present study, however, the investigators found no association between AVC and mortality. This finding can be explained by the fact that 169 of the 214 patients (79%) in this cohort underwent aortic valve intervention, which has changed the natural history of the disease.

The most important limitation of this study is the reference method used to define AS severity. The investigators indeed used DSE and a single criterion (ie, stress AVA <1.0 cm^2) to define truly severe AS.[3] An analysis of the multicenter TOPAS (Multicenter Prospective Study of Low-Flow Low-Gradient Aortic Stenosis) study showed that among patients with classical low-flow, low-gradient AS, DSE is nondiagnostic in about 55% because of absent or limited flow reserve.[9] In that study, the sensitivity and specificity of this DSE criterion (stress AVA <1.0 cm^2) were 63% and 56%, respectively, and the area under the receiver-operating characteristic curve was 0.60 ($P = 0.07$) (Figure 1).[9] Hence, the low diagnostic accuracy of AVC reported in the present study[3] might be attributable in large part to low accuracy of the reference method, DSE.

In light of the results of previous studies, it is likely that peak stress AVA measured using DSE is actually inferior to MSCT-derived AVC to identify truly severe AS. In the TOPAS study, the diagnostic accuracy of other DSE parameters, such as stress MG ≥40 mm Hg (sensitivity, 35%; specificity, 65%; area under the curve, 058) was also low and even worse than that of stress AVA (Figure 1).[9] The main reason for the limited diagnostic value of these stress echocardiographic parameters is that they are highly flow dependent and that the flow response to dobutamine stress is highly variable from one patient to another. Indeed, only 45% of patients exhibit flow reserve and are therefore able to reach normal flow range during DSE. Because the majority of patients remain in a low-flow state, the discordant grading (ie, small AVA with a low gradient) that is observed on rest TTE often persists on DSE. Also, some patients, especially those with preserved LVEFs (18% in the present cohort), may develop supranormal flow rates during DSE, and in the situation of a high-flow state, stress AVA may underestimate and stress MG overestimate AS severity. The only dobutamine stress echocardiographic parameter

FIGURE 2 **Multimodality, Multiparameter Integrative Approach to Adjudicate Severity and Indication of Intervention in Patients With Low-Gradient AS**



Note that this is hypothesis generating and is not recommended in current guidelines. AS = aortic stenosis; AU = Agatston units; AVA = aortic valve area; AVAi = indexed aortic valve area; AVR = aortic valve replacement; LG = low-gradient; LVEF = left ventricular ejection fraction; MG = mean transvalvular pressure gradient; SV = stroke volume; SVi = stroke volume index; TTE = transthoracic echocardiography.

that overcomes this limitation of flow dependency is the projected AVA at a normal flow rate, which has been shown to be superior to peak stress AVA, peak stress MG, and their combination to identify truly severe AS and predict prognosis in patients with low-flow, low-gradient AS (**Figure 1**).[9] In the TOPAS study, although the projected AVA was superior to other dobutamine stress echocardiographic parameters, it nonetheless had suboptimal performance, with a percentage of overall correct classification of 68%.[9] In the present study, the investigators present a subanalysis with the projected AVA, but it is unclear in which proportion of the patients this variable was available and which cutpoint was used to identify severe AS.[3]

In conclusion, TTE, DSE, and MSCT should not be considered competitive or substitutive diagnostic methods but rather complementary and synergistic in the adjudication of AS severity. These methods are not equivalent and actually measure different but complementary parameters of AS severity. Indeed, TTE assesses the hemodynamic severity of AS at rest and thus often in low-flow-state conditions, whereas DSE assesses hemodynamic severity under dobutamine stress and thus in variable-flow-state conditions. MSCT quantitates the anatomical severity of AS, which is independent of flow conditions. Each method and each parameter has inherent strengths and also pitfalls and limitations. Hence, a multimodality, multiparameter integrative approach should be applied to confirm AS severity in patients with low-gradient AS, as illustrated in **Figure 2**. In patients with classical low-flow, low-gradient AS, who represented the vast majority of the cohort in the present study,[3] DSE should be used as the first-line diagnostic test, and MSCT should be considered if

JACC: CARDIOVASCULAR IMAGING, VOL. 17, NO. 8, 2024
AUGUST 2024:861–864

DSE is inconclusive, which may occur in up to 55% of the cases (Figure 2). In patients with paradoxical low-flow, low-gradient and in those with normal-flow, low-gradient AS, DSE is not the optimal test, and MSCT should be considered as the first-line test.

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 computed tomography 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 holds the Canada Research Chair in Women's 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 G1V 4G5, Canada. E-mail: philippe.pibarot@med.ulaval.ca. X handle: @ppibarot.

REFERENCES

1. 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.

2. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler-echocardiographic and computed tomographic study. *J Am Coll Cardiol*. 2013;62:2329–2338.

3. Adrichem R, Hokken TW, Bouwmeester S, et al. Diagnostic value of aortic valve calcification levels in the assessment of low-gradient aortic stenosis. *JACC Cardiovasc Imaging*. 2024;17(8):847–860.

4. Pawade T, Sheth T, Guzzetti E, Dweck MR, Clavel MA. Why and how to measure aortic valve calcification in patients with aortic stenosis. *JACC Cardiovasc Imaging*. 2019;12:1835–1848.

5. Eberhard M, Mastalerz M, Frauenfelder T, et al. Quantification of aortic valve calcification on contrast-enhanced CT of patients prior to transcatheter aortic valve implantation. *EuroIntervention*. 2017;13:921–927.

6. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol*. 2014;64:1202–1213.

7. Powers A, Ali M, Lavoie N, et al. Aortic valve calcification density measured by MDCT in the assessment of aortic stenosis severity. *Circ Cardiovasc Imaging*. 2024;17:e016267.

8. Tastet L, Enriquez-Sarano M, Capoulade R, et al. Impact of aortic valve calcification and sex on hemodynamic progression and clinical outcomes in AS. *J Am Coll Cardiol*. 2017;69:2096–2098.

9. Annabi MS, Touboul E, Dahou A, et al. Dobutamine stress echocardiography for management of low-flow, low-gradient aortic stenosis. *J Am Coll Cardiol*. 2018;71:475–485.

KEY WORDS aortic stenosis, aortic valve replacement, computed tomography, Doppler-echocardiography, hemodynamics, stress echocardiography