JACC: ADVANCES VOL. 3, NO. 4, 2024

EDITORIAL COMMENT

Moderate Aortic Stenosis Progression

When Do We Reassess?*

Deepa Raghunathan, MD,[a] Anju Bhardwaj, MD[b]

Calcific aortic stenosis (AS) is the most common valvular disease in Western countries, and its incidence continues to rise, potentially due to the relative ease of diagnosis as well as the increase in noncardiac comorbidities in our aging population.[1,2]

Echocardiography remains the first-line imaging modality to diagnose, quantify, and monitor the progression of AS with 2-dimensional (2D) anatomic (geometric) evaluation of the leaflet excursion and with valvular hemodynamic assessment.[2] Severe AS is defined as a peak velocity (PV) across the aortic valve (AV) >4 m/s, mean gradient >40 mm Hg, and aortic valve area (AVA) <1 cm^2. When imaging suggests severe AS, AV replacement is recommended, ideally before clinical symptoms occur or prior to left ventricular dysfunction.[3] Moderate AS is defined as PV 3 to 3.9 m/s, mean gradient 20 to 39 mm Hg, and AVA 1.0 to 1.4 cm^2.[4] However, valve replacement for moderate AS is recommended when patients are undergoing cardiac surgery for another indication.[3] Though more frequent echocardiography is recommended when the PV is close to severe (every 1-2 years for moderate AS, every 6-12 months for severe AS), long-term mortality with untreated moderate AS is similar to that with untreated severe AS.[3,5] This finding raises the possibility that we are missing patients who would benefit from interventions sooner or that we may be misclassifying aortic disease with each longitudinal study. Therefore, identifying individuals with higher rates of AS progression might allow for optimal patient-specific timing of follow-up echocardiograms.

In this issue of *JACC: Advances*, Venema et al[6] suggested a patient-specific model to predict the progression rate of AS, thereby identifying patients at higher risk of rapid progression and suggesting a tailored approach for their follow-up. In this single-center, retrospective study, they identified patients with moderate AS over an 11-year period and ensured at least 2 serial echocardiograms were available during that period to assess progression from AS. The majority of patients in this study were men and had a normal left ventricular (LV) function and stroke volume (SV) index. The rate of progression was considered "rapid" if the median annual AVA decrease was 0.15 $cm^2$and "slow" if the median annual AVA change was 0.04 cm^2 decrease per year. The findings suggested a linear decrease in AVA over time, at a median rate of 0.09 cm^2/year. Via a linear mixed-effects analysis, those who progressed rapidly to severe AS were older, had baseline atrial fibrillation, chronic kidney disease, a higher baseline LV mass index, and a higher baseline SV index. Rapid reduction in AVA was associated with higher mortality rates and increased rates of hospitalization due to heart failure.

In this study, AVA was the primary parameter used to assess the progression of AS. The AVA in this study was calculated using the continuity equation, which is significantly dependent on left ventricular outflow tract (LVOT) diameter as it assumes the LVOT is circular and can result in an underestimation of the AVA calculated.[7] To minimize interobserver variability longitudinally, Venema et al[6] used a median LVOT diameter for each patient. The continuity equation also utilizes the LVOT velocity time integral or LVOT PV, which is dependent on the location of the pulse-wave Doppler within the LVOT. This parameter is

*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 [a]Division of Cardiology, Department of Medicine, University of Texas Health Science Center at Houston, Houston, Texas, USA; and the [b]Center for Advanced Cardiopulmonary Therapies & Transplantation, University of Texas Health Science Center at Houston, Houston, Texas, USA.

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 2772-963X https://doi.org/10.1016/j.jacadv.2024.100882

difficult to minimize interobserver error longitudinally and therefore can affect the changes in AVA seen in this study. LVOT area can be directly planimetered for the continuity equation via 3-dimensional echocardiography and multidetector computed tomography, but there is conflicting data regarding the correlation between the 2 imaging modalities.[8,9] Furthermore, multidetector computed tomography-calculated AVA or AVA by planimetry does not provide prognostication as predicted by echocardiographic Doppler assessment and is not recommended to classify the severity of AS.[4]

It should be noted that previous studies have identified similar rates of progression of AVA, PV, and gradients.[10] Nonetheless, this study assumes a linear progression of AVA decrease and extrapolates rates of decrease with certain baseline characteristics. This finding could potentially allow for more personalized timing of follow-up echocardiograms. The amount of maladaptive LV remodeling seen with longstanding AS results in LV systolic and diastolic dysfunction, which sways the timing of AV replacement.[3] Global longitudinal strain and strain rate can detect LV dysfunction prior to changes seen in 2D alone, but in this study, LV remodeling was assessed predominantly with 2D parameters.[11] With most patients included in this study having preserved LV ejection fraction, using additive LV assessments might have reclassified the rate of AS progression.

Notably, more than one-half of the patients in this study were men; however, AV anatomy and cardiac remodeling vary between the genders. Women tend to have less aortic calcification than men for the same hemodynamic severity of AS.[12] The LV remodeling seen in women results in smaller LV volumes compared to men and therefore, smaller LVOT diameters and SV. The discrepancy may explain the increased prevalence of paradoxical low-flow AS with preserved left ventricular ejection fraction seen in women.[12] Conversely, the smaller AVA calculated in women may also overestimate the severity of AS in women, even after correcting for body surface area.[13] These gender differences in AVA assessment limit the applicability of the presented study across all moderate AS patients.

Given the need for accurate classification of AS by imaging, there could be a role for machine learning and artificial intelligence. In echocardiography, artificial intelligence has been shown to correlate with human measurements of standard AS Dopplers parameters.[14] It may allow for less interobserver variability when performing surveillance echocardiograms, particularly when measuring the LVOT diameter. Machine learning has also proven to be useful, particularly for those with discordant echocardiographic findings. It has been shown to accurately identify traditionally severe AS as high-severity AS but also reclassify traditionally non-severe AS to the high-severity group as well, for potentially more accurate risk stratification in this subgroup.

There is no proven medical or surgical treatment for moderate AS thus far. But with trials underway like EXPAND TAVR II (NCT05149755) and PROGRESS (NCT04889872) to investigate the role of early intervention for patients with symptomatic moderate AS, the importance of early and accurate detection of the progression of moderate AS is even more critical. The authors should be applauded for their work on clinical progression of moderate AS, as they identified several clinical factors that were associated with a more rapid progression of disease. There are several limitations with our current methods to monitor the progression of AS, and Venema et al[6] suggest parameters that may be used to personalize the timing of follow-up echocardiographic studies. This model takes us closer to creating a patient-specific AS progression rate calculator and may tailor timing to assess AS progression. Furthermore, these parameters may help us recognize patients for future trials to investigate therapies that will delay the progression of moderate AS. But for now, this remains an aspirational goal, and we are left with the current echocardiographic tools as we try to monitor the progression of moderate AS.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Anju Bhardwaj, Division of Advanced Cardiopulmonary Therapies and Transplantation, Department of Cardiovascular Medicine, McGovern Medical School/University of Texas Health Sciences Center, 6400 Fannin Street, Suite 2350, Houston, Texas 77004, USA. E-mail: anju.bhardwaj@uth.tmc.edu.

REFERENCES

1. Isselbacher EM, Preventza O, Black JH, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American heart association/American College of Cardiology Joint Committee on clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;80(24):e223–e393.

2. Manzo R, Ilardi F, Nappa D, et al. Echocardiographic evaluation of aortic stenosis: a comprehensive review. *Diagnostics (Basel)*. 2023;13:2527.

3. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American heart association Joint Committee on clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77(4):e25–e197.

4. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a Focused Update from the European association of Cardiovascular imaging and the American Society of echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392.

5. Strange G, Stewart S, Celermajer D, et al. Poor long-term Survival in patients with moderate aortic stenosis. *J Am Coll Cardiol*. 2019;74:1851–1863.

6. Venema CS, van Bergeijk KH, Hadjicharalambous D, et al. Prediction of the individual aortic stenosis progression rate and its association with clinical outcomes. *JACC: Adv*. 2024;3:100879.

7. Hahn RT, Pibarot P. Accurate measurement of left ventricular outflow tract diameter: comment on the updated recommendations for the echocardiographic assessment of aortic valve stenosis. *J Am Soc Echocardiogr*. 2017;30:1038–1041.

8. Gaspar T, Adawi S, Sachner R, et al. Three-dimensional imaging of the left ventricular outflow tract: impact on aortic valve area estimation by the continuity equation. *J Am Soc Echocardiogr*. 2012;25:749–757.

9. Clavel MA, Malouf J, Messika-Zeitoun D, Araoz PA, Michelena HI, Enriquez-Sarano M. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. *J Am Coll Cardiol Img*. 2015;8:248–257.

10. Willner N, Prosperi-Porta G, Lau L, et al. Aortic stenosis progression: a systematic review and Meta-analysis. *J Am Coll Cardiol Img*. 2023;16:314–328.

11. Rassi AN, Pibarot P, Elmariah S. Left ventricular remodelling in aortic stenosis. *Can J Cardiol*. 2014;30:1004–1011.

12. Cramariuc D, Bahlmann E, Gerdts E. Grading of aortic stenosis: is it more complicated in women? *Eur Cardiol*. 2022;17:e21.

13. Cotella JI, Miyoshi T, Mor-Avi V, et al. Normative values of the aortic valve area and Doppler measurements using two-dimensional transthoracic echocardiography: results from the Multicentre World Alliance of Societies of Echocardiography Study. *Eur Heart J Cardiovasc Imaging*. 2023;24:415–423.

14. Krishna H, Desai K, Slostad B, et al. Fully Automated artificial intelligence assessment of aortic stenosis by echocardiography. *J Am Soc Echocardiogr*. 2023;36:769–777.

KEY WORDS aortic stenosis, aortic valve area, moderate