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EDITORIAL COMMENT

# Aortic Stenosis and Cardiac Amyloidosis

## Watch Out for Traps!*

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The prevalence of transthyretin cardiac amyloidosis (TTR-CA) increases with age and has been reported to be ~10% to 15% in ≥65-year-old patients with heart failure; this condition is more prevalent in African Americans (1). Similarly, calcific aortic stenosis (AS) is the most frequent valvular heart disease in high-income countries, and its prevalence also increases with age. In addition, AS is associated with left ventricular hypertrophy and dysfunction, similar to that observed in TTR-CA. Hence, AS and TTR-CA frequently coexist in older adults and share several clinical and echocardiographic features. These similarities complicate the diagnosis and management of both conditions. The indication for aortic valve replacement in patients with AS is essentially determined by the presence of severe AS and of symptoms and/or left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <50%). However, symptoms are nonspecific and can be related to AS, TTR-CA, or both. Furthermore, the presence of TTR-CA may alter LV systolic function and outflow and thus raise uncertainty regarding the actual severity of AS and the indication for intervention.

The accumulation of amyloid fibrils within the myocardium results in wall thickening and stiffening, which lead to restrictive cardiomyopathy with both LV and right ventricular dysfunction. LVEF is often preserved in patients with TTR-CA, but low cardiac output and thus a low transvalvular flow state are frequent and may complicate the evaluation of AS severity. Discordant grading of AS severity on echocardiography is defined by an aortic valve area ≤1 $cm^2$ or ≤0.6 $cm^2/m^2$ after indexation to body surface area associated with a low transvalvular velocity and gradient (peak velocity <4 m/s and mean gradient <40 mm Hg) and can be explained by the low-flow state (i.e., stroke volume indexed to body surface area <35 $ml/m^2$) related to the biventricular dysfunction. This low-flow, low-gradient (LF-LG) pattern of severe AS can be observed in up to 80% of patients with TTR-CA (2). In cases of discordant AS grading, European guidelines recommend confirming AS severity by using dobutamine stress echocardiography and/or aortic valve calcium (AVC) score quantification by noncontrast computed tomography (CT) (3).

The case series reported in this issue of *JACC: Case Reports* by Hussain et al. (4) reports 3 patients with concomitant AS and TTR-CA who presented with evidence of severe AS on echocardiography or dobutamine stress echocardiography but in who had noncontrast CT revealing AVC scores below severity cutoffs proposed in the guidelines (>1,200 AU in women and >2,000 AU in men). These intriguing findings may be explained by the following: 1) overestimation of AS severity by echocardiography because of the low-flow state and ensuing LF-LG pattern related to TTR-CA and/or AS; and/or 2) underestimation of AS severity by noncontrast CT because of the potentially distinctive pathophysiological process of AS in the context of TTR-CA. Some studies indeed suggest that amyloid substance may deposit within the aortic valve leaflets and thus lead to the development of AS despite absent or minimal leaflet calcification (5,6). In such cases, noncontrast

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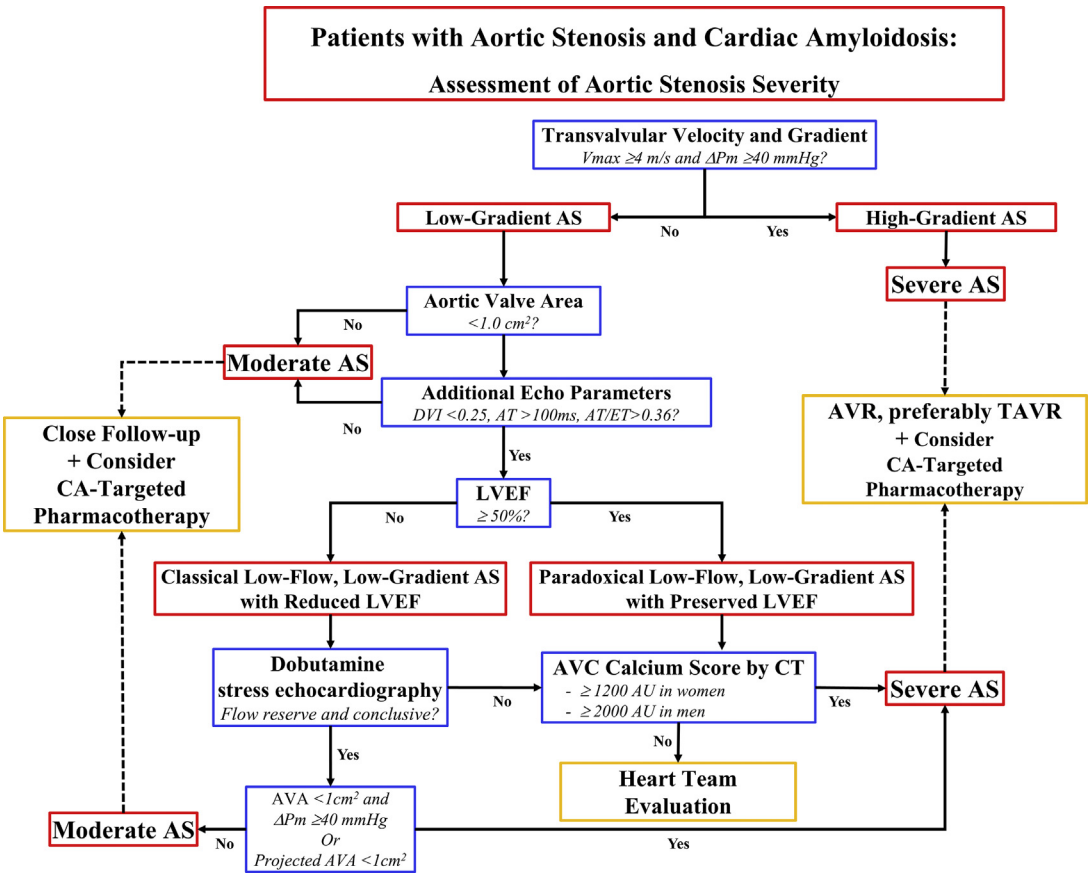
**FIGURE 1** Proposed Algorithm for Aortic Stenosis Severity Confirmation and Management in Patients With Transthyretin CA




AS = aortic stenosis; AT = acceleration time; AT/ET = ratio of acceleration time over ejection time; AU = Agatston unit; AVA = aortic valve area; AVC = aortic valve calcium; AVR = aortic valve replacement; CA = cardiac amyloidosis; CT = computed tomography; DVI =: Doppler velocity index; LVEF = left ventricular ejection fraction; TAVR = transcatheter aortic valve replacement; Vmax = aortic valve peak velocity; *ΔPm* = mean pressure gradient.

CT, which captures only the calcified component of the valve leaflet tissue, would underestimate the severity of this amyloid-related AS. Hence, this report raises an important question: How do we confirm the diagnosis of severe AS accurately in patients with TTR-CA and discordant echocardiographic grading?

In patients with LF-LG pattern and thus discordant AS grading, additional echocardiographic parameters, including the dimensionless (or Doppler) velocity index, the acceleration time (AT), and its ratio over ejection time (AT/ET), and the assessment of valve leaflet morphology and mobility, have been proposed to corroborate stenosis severity (7–9). However, these echocardiographic parameters are also influenced by LV function and flow and may thus not provide accurate and definitive grading of AS severity. Dobutamine stress echocardiography may be used to confirm the presence of true or severe AS in patients with a classical (low LVEF) LF-LG pattern, such as Patient #1 in the present series (4). However, this test is not conclusive in patients with classical LF-LG with no LV contractile or flow reserve and is not appropriate for patients with paradoxical LF-LG AS (such as Patients 2 and 3 in the present series). In such patients, who may represent an important proportion of patients with AS and concomitant TTR-CA, the AVC score measured by noncontrast CT may be helpful to confirm the presence of severe AS and thus the indication for intervention. However, the AVC thresholds proposed in the guidelines have not been validated in the context of TTR-CA. The present series suggest that such patients may have a form of AS with minimal valve calcification, in

which the valve leaflet thickening and stiffening are related more to the amyloid deposit rather than to the calcification. Noncontrast CT allows only the quantitation of the mineralized tissue and would thus underestimate stenosis severity in this context. Future perspectives in this field include the use of contrast CT that would allow the quantitation of both calcified and noncalcified (e.g., fibrosis, amyloid) leaflet tissues contributing to the AS. Pending these future developments, a multimodality, multiparameter integrated approach and comprehensive evaluation by the heart team should be adopted to confirm presence of severe AS and the indication for intervention in patients with AS and TTR-CA (**Figure 1**). The role of the heart team in this challenging subset of patients with AS is crucial: 1) to confirm AS severity in the presence of discordant grading on echocardiography and/or CT; and 2) if the presence of severe AS is confirmed, to determine the best therapeutic option among medical management (including CA-targeted pharmacotherapies), surgical aortic valve replacement, or transcatheter aortic valve implantation.

Following initial reports in small numbers of patients with AS and advanced TTR-CA that revealed a high rate of futility of aortic valve replacement (10,11), a more recent and larger registry with more systematic screening of TTR-CA suggested overall good outcomes following valve intervention. Hence, aortic valve replacement should not be avoided or discouraged in symptomatic patients with TTR-CA who have evidence of severe AS on echocardiography and/or CT. Furthermore, regardless of the decision to perform aortic valve replacement or to forgo it, the heart team should discuss the relevance and options of new pharmacotherapies targeting TTR-CA (**Figure 1**).

In conclusion, Hussain et al. (9) should be congratulated for raising our awareness of the pitfalls of CT for the assessment of AS severity and the risk of underestimating AS severity in patients with concomitant TTR-CA. Further studies in patients with TTR-CA are urgently required to determine which imaging modalities and parameters are most appropriate to confirm AS severity and the indications for intervention in patients with AS and concomitant TTR-CA.

## AUTHOR DISCLOSURES

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