Low-Gradient Severe Aortic Stenosis With Preserved Ventricular Function

Trust But Verify*

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Valvular aortic stenosis (AS) has been recognized for decades as a progressive valvular disease that carries significant morbidity and mortality. In normal flow conditions, AS is defined as severe when the mean transvalvular pressure gradient is ≥40 mm Hg and the valve area is reduced below 1 cm² (<0.8 cm² for more specificity) (1). Because of the dependency of gradients on flow, lower gradients may be seen with severe aortic stenosis (SAS) in reduced flow conditions, be it in the presence of depressed or normal left ventricular (LV) function. Low-gradient severe aortic stenosis (LGSAS) with preserved LV ejection fraction (EF) has been highlighted since 2007 (2) as an entity that portends a poor prognosis, with few inconsistencies. In this issue of the Journal, Dayan et al. (3) report a meta-analysis of studies on the clinical outcome and impact of aortic valve replacement (AVR) in patients with LGSAS and preserved EF that summarizes the current knowledge of this entity and its implications as to the patient substrate, prognosis, and management.

The authors conducted a thorough and rigorous meta-analysis; however, it is the robustness of the individual studies that ultimately affects the overall results and conclusions of such analysis. Of the 18 studies included, various comparisons of either prognosis or effect of AVR could be performed in a subset of these reports. All investigations were retrospective, nonrandomized, and unmatched, with the exception of the echo substudy of the PARTNER (Placement of Aortic Transcatheter Valves) trial (4), where the population was defined prospectively and randomized per treatment strategy; coronary artery disease requiring revascularization, a determinant of outcome and a confounding variable in most reports, was excluded from the study. No individual data were available to adjust for confounding variables and the duration of follow-up was variable. Despite these limitations, the current investigation sheds light on the entity of LGSAS.

LGSAS WITH PRESERVED LV EF

This hemodynamic situation can arise from different clinical conditions and causes, including a low-normal or mildly reduced stroke volume in patients

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with normal LV size and borderline or mildly depressed LV systolic function, a small LV related to a small body size and/or concentric hypertrophy or remodeling yielding a lower stroke volume, calculation errors in determining stroke volume and valve area by Doppler echocardiography (underestimation of LV outflow diameter because of its shape or calcifications, or malposition of the Doppler sample volume), and an internal inconsistency in the definition of SAS by current guidelines relating to the cutoff of valve area in relation to gradient and jet velocity (1 cm² cutoff is sensitive but less specific for hemodynamically SAS, whereas 0.8 cm² corresponds more closely to the gradient/velocity cutoffs of SAS). In the meta-analysis, patients with low-flow LGSAS had overall clinical characteristics that were consistent among studies: compared with high-gradient SAS, they were older and had a higher prevalence of coronary artery disease, diabetes mellitus, and hypertension. As such, low-flow LGSAS with preserved LVEF is a clinical condition that is frequently accompanied by comorbidities that inherently have an impact on prognosis and may explain, at least in part, the worse outcome observed.

In this spectrum of LGSAS, those with normal flow and preserved LVEF represent another heterogeneous group as acknowledged by the authors, because their valve area is likely higher than those with low-flow LGSAS. Many of these patients have pseudo-SAS, because their valve area usually is just below 1 cm². Of interest, in the current study, the high prevalence of comorbidities in this population was similar to those with low-flow LGSAS and may in part account for the comparable prognosis of these 2 patient populations. Ascertainment severity of AS in LGSAS is crucial for patient management; asymptomatic patients can be managed medically until symptoms arise, because their prognosis may be similar to moderate AS in the setting of lesser AS severity and fewer comorbidities (7).

**EFFECT OF AVR ON PROGNOSIS IN LGSAS**

AVR in patients with SAS improves survival in symptomatic patients. In the current study, AVR improved survival compared with conservative therapy in patients with LGSAS (low and normal flow); however, patients with high-gradient SAS, who also had fewer comorbidities, had the greatest benefit. With the limitations to the studies already noted, the question is whether the survival benefit is overestimated because the populations were not matched or randomized, leaving the medically treated cohorts with more comorbidities and higher overall risk for the same severity of AS. However, this cannot be resolved from the current analysis. The echo sub-study of the PARTNER trial provides at present the best investigation to evaluate the comparative effect of AVR versus medical therapy on outcome in symptomatic patients with LGSAS who had sufficient comorbidities and risk to be deemed inoperable (4). Valve area was severe at entry (<0.8 cm²). Outcome with AVR was clearly superior to conservative treatment; low flow was the most important prognostic imaging parameter in all patients (4). Although most studies were not controlled, the findings from the meta-analysis are still consistent with current guidelines for a IIa recommendation for AVR in symptomatic patients with LGSAS (1).

In the meta-analysis, studies that included patients with moderate AS (valve area >1 cm²) raise a concern of patient selection: 59% had symptoms similar to or higher than those with SAS, and 35% of them underwent AVR. This is an unusually high prevalence of symptoms and AVR in moderate AS and should not be extrapolated to the AS population at large, because moderate AS has been shown to have an intermediate prognosis. Of interest is that in the 2 studies where AVR was compared with medical therapy in moderate AS, there was no advantage of AVR, as would be expected.

**TRUST BUT VERIFY**

Patients with LGSAS present a diagnostic and therapeutic challenge to the clinician. The terminology can be complicated, because it incorporates measurements of gradient, flow, LVEF, and valve area. Although cutoffs have been proposed for what constitutes low-flow, LG, and severe valve area, the clinician should realize the continuum in AS disease and the frequent straddling of these parameters in a particular patient. It is important to recognize that patients with LGSAS can be asymptomatic, and their prognosis may be similar to moderate AS if their valve area is moderately severe and they have few comorbidities. In the symptomatic patient, ascribing symptoms to an underlying etiology may be challenging because symptoms may be related to the comorbidities and/or the AS. Furthermore, not all patients with “severe” AS are created equal. The smaller the valve area in patients with LGSAS, the more confident one is of the severity of the disease, its related symptoms, and the need for an intervention.

In LGSAS with preserved LVEF, and particularly in low-flow conditions, ascertaining the severity of AS is of paramount importance. Because Doppler
echocardiography is the main first-line diagnostic modality, the echocardiographer needs to ensure that the data on quantitated flow and derived valve area are internally consistent with low flow through the AS (e.g., small LV volume, concomitant mitral regurgitation, and so forth). If inconsistencies occur and cannot be resolved, they should be communicated to the clinician and additional testing suggested for further evaluation of AS severity, such as dobutamine echocardiography, cardiac magnetic resonance, computed tomography, or invasive hemodynamics, as deemed appropriate—another facet of the heart team approach to cardiac care in valvular heart disease.

REFERENCES

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