Accurate assessment of aortic stenosis (AS) severity is one of the more technically demanding studies in echocardiography. This is reflected in the Intersocietal Accreditation Commission for Echocardiography standards that specify that AS gradients must be measured from at least 3 different transducer positions and with a nonimaging, dedicated, continuous-wave Doppler transducer (Pedhoff). The standards do not specify the measurement of any other valvular lesion. Submission and review of AS cases is required for laboratory accreditation by that body. Given the complexity in echocardiographic assessment, the determination that a patient has severe AS (defined as a valve area \( \leq 1 \text{ cm}^2 \) or an indexed area \( \leq 0.6 \text{ cm}^2/\text{m}^2 \)) but a mean gradient \( <40 \text{ mmHg} \) despite a preserved left ventricular (LV) ejection fraction (LVEF) is often met with skepticism by our interventional colleagues. Low-gradient severe AS resulting from decreased LV systolic function can be assessed by dobutamine protocols intended to increase the flow across the valve and to distinguish true AS from pseudo-AS.1 Such is usually not the case in patients with preserved LVEF.

Work by a group in Quebec has highlighted the existence of paradoxical low-gradient severe AS (LGSAS) in patients with preserved LVEF but paradoxically low stroke volume.2 The low stroke volume is presumably attributable to a small LV cavity that has been infringed on by LV hypertrophy and decreased myocardial function that has not yet resulted in a decreased LVEF. Milano et al3 performed intraoperative myocardial biopsies on patients undergoing aortic valve replacement (AVR) for AS and demonstrated that those patients with moderate fibrosis had much poorer long-term outcome despite normal LVEF compared with patients with no or mild fibrosis. Other groups have confirmed fibrosis and myocardial dysfunction in these patients with magnetic resonance imaging to assess fibrosis and echocardiographic strain imaging to evaluate myocardial performance.4,5 In an important study published earlier this year, investigators confirmed that LGSAS with preserved LVEF was not attributable to systematic error in the echocardiographic assessment.6 They reviewed the echocardiographic and invasively obtained hemodynamic data on 58 patients with LGSAS and preserved LVEF at their institution and compared them with a group of 22 patients with conventionally defined AS (valve area \( \leq 1 \text{ cm}^2 \), mean transvalvular gradient \( \geq 40 \text{ mmHg} \)). Invasive gradients were determined by pullback with manual tracing of the gradients, and stroke volume was assessed by both oximetry (using a nomogram for oxygen consumption) and thermodilution. Reclassification of patients with severe AS by echocardiography to moderate AS occurred in only 1 of 58 patients using thermodilution stroke volume and in just 10% of the patients using oximetry. Reclassification occurred in 4% of patients with conventionally defined AS. Interestingly, although most of the LGSAS patients had an abnormally low stroke volume, 10% did not. Of the conventional AS group, 18 of 22 also had low stroke volume. This careful comparison of hemodynamic and echocardiographic data confirms that LGSAS with preserved LVEF and low or normal stroke volume is not a figment of the echocardiographer’s imagination but an important clinical entity.

An understanding of this controversy highlights the importance of the article in this issue of Circulation by Ozkan et al,7 which makes the strong case that LGSAS with preserved LVEF is best treated by AVR. Because the gradients across a bioprosthetic valve may approach the level of gradients seen in patients with LGSAS, there is often hesitancy to offer this group surgery or transcatheter replacement. Ozkan et al identified 260 patients with preserved LVEF and LGSAS in the entire cohort of 1588 patients with symptomatic severe aortic stenosis seen at their institution between 2006 and 2011. All patients were symptomatic. This is an observational study, and the treatment was decided on by the treating team. If the patient underwent surgery, the type of surgery (conventional surgical AVR or transcatheter AVR) was determined by the same team. There was complete follow-up of both groups for all-cause mortality with follow-up over an average of 28±24 months. The authors used propensity score (PS) analysis to determine the possible benefit of AVR. PS is an attempt to account for baseline differences between treated and untreated subjects to estimate the treatment effect (see below). Their results demonstrate that the medically treated group had a 2-fold increased risk of mortality compared with those who underwent AVR of either type.

The study group included both patients with low stroke volume indexes (SVIs; \(<35 \text{ mL/m}^2\)) and those with normal SVIs. In the entire group, there were 125 patients with normal SVI and 135 with low SVI. The low-SVI patients had slightly
lower LVEF although still in the normal range, lower mid-wall fractional shortening (a measure of myocardial function), and smaller aortic valve areas, along with higher LV afterload. Surgical patients had a higher stroke volume on average, and there were more low-SVI patients in the medically treated group. After the PS analysis, it was shown that both low-flow and normal-flow patients treated medically had a 2-fold greater all-cause mortality compared with the AVR group. This is a very important finding. Although other studies have generally found a mortality benefit in AVR in patients with LGSAS with preserved LVEF, none accounted as carefully for the significant differences in baseline characteristic between the 2 groups. It is well known that medical therapy for symptomatic severe AS carries a terrible prognosis. The group of patients with LGSAS with preserved LVEF may have an even worse prognosis because the low gradient in general appears to reflect subclinical myocardial dysfunction. It is gratifying that this group can be offered AVR with an expectation of improvement in mortality. In this study, there was no difference in mortality for the medically treated patients with low or normal SVI. The recently released European guidelines rate AVR in the LGSAS group as a Class IIa indication (Level of Evidence, C). They caution that the diagnosis of severe AS should be carefully confirmed. Each laboratory is of course responsible for the quality of its assessments. Although catheterization is considered a Class III indication (should not be performed) for the assessment of AVA in patients with severe AS by echocardiography, this group of patients represents an exception to that rule.

PSs have been increasingly used to analyze observational data in an attempt to approximate a randomized trial. In the study by Ozkan et al, the differences between the surgical and medically treated groups were substantial. The surgical group was demonstrably healthier with fewer instances of diabetes mellitus, better renal function, fewer instances of hypotension, and less diuretic use. Because the healthier group of patients underwent surgery, on the face of it, it is not surprising that AVR was associated with lower mortality. Although there are several methods for PS, in a relatively small group with marked differences in characteristics, the usual way to determine the PS is to perform a logistic regression with treatment, in this case AVR, as the dependent variable. Because many of the clinical factors influence both treatment assignment and outcome, these clinical factors are all included in the logistic regression. The PS is then the likelihood of treatment assignment conditional on the baseline characteristics. The PS is entered into Cox multivariate models along with other clinical variables to estimate the treatment effect. As with all logistic regressions, there must be no unmeasured confounders, or the results will not be accurate. The authors rightly note that such unmeasured characteristics as frailty, severe chronic obstructive pulmonary disease, or dementia may have played a role in treatment selection and outcome.

How reliable is the method in general? In a recent analysis by Dahabreh et al, the results of observational studies using PS and randomized, clinical trials were compared in the studies of treatments in patients with acute coronary syndromes. They found that the estimates of treatment effect on mortality were consistent between randomized, clinical trials and PS studies. In only 2 of the 17 separate comparisons was there a statistically significant difference in treatment effect. However, the PS studies systematically overestimated the magnitude of the treatment effect found in the randomized, clinical trial of the same therapy. Thus, it must be cautioned that the finding that AVR substantially reduces mortality in the present article may be an overestimate of the true benefit.

In conclusion, this article is an important contribution to our growing understanding of the group of patients with severe AS and low transvalvular gradients despite preserved LVEF. It goes without saying that a randomized, controlled trial in this group of largely elderly patients with multiple comorbidities is unlikely to be conducted, particularly when medical therapy has been shown to have so dismal an outcome. Ozkan et al expand our understanding of the entity of LGSAS and make a powerful case for surgical intervention for symptomatic patients.

Disclosures
None.

References


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Symptomatic Low-Gradient Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction: Now Less of a Clinical Conundrum
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