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EDITORIAL COMMENT

The Complex Interaction Between Left Ventricular Ejection Fraction, Flow, and Gradient in Patients Undergoing TAVR*

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The 2014 American College of Cardiology/American Heart Association guidelines (1) recommend (class I) aortic valve replacement (AVR) in patients with high aortic valve gradient (mean gradient ≥40 mm Hg) severe aortic stenosis (AS) who have symptoms, reduced left ventricular (LV) ejection fraction (EF <50%), and/or undergo another cardiac surgery. However, an important proportion (≤50%) of patients with AS have a "low-gradient" form of the disease, which is defined as the combination of a small aortic valve area (AVA <1.0 cm^2) consistent with severe AS and a low gradient (<40 mm Hg) consistent with nonsevere AS (**Figure 1**). The gradient is highly flow-dependent and therefore the most frequent cause of low-gradient AS is the presence of a low LV outflow state (stroke volume index <35 ml/m^2), which may occur with reduced LVEF (i.e., classical low-flow, low-gradient), or with preserved LVEF (i.e., paradoxical low-flow, low-gradient) (2). In classical low-flow, low-gradient AS, the reduction in stroke volume and thus transvalvular flow is predominantly related to depressed LV systolic dysfunction, whereas in paradoxical low-flow, low-gradient AS, pronounced LV concentric remodeling and impaired diastolic filling are the main mechanisms responsible for the reduced stroke volume. Other factors such as atrial fibrillation, concomitant mitral regurgitation, mitral stenosis, or tricuspid regurgitation, which are highly prevalent in the elderly population with AS, also may contribute to the low flow state in both types (classical and paradoxical) of low-flow, low-gradient AS.

Management of patients with low-gradient AS is very challenging because, at resting echocardiography or catheterization, these patients have the combination of a small AVA with a low gradient, which raises uncertainty about the actual stenosis severity and thus the indication of AVR (**Figure 1**) (2). Additional tests such as assessment of aortic valve morphology and motion by 2-dimensional (2D) transthoracic or transesophageal, dobutamine stress echocardiography, or aortic valve calcium scoring by multidetector computed tomography are often required in these patients to confirm AS severity and the need for AVR (**Figure 1**) (2–4). Furthermore, the presence of a low gradient is often the marker for a low-flow state and associated comorbidities mentioned previously. These factors may increase the risk of complications and cardiac events during and after AVR. In the 2014 American College of Cardiology/American Heart Association guidelines (1), high-gradient AS is classified as a D1 stage of the disease, whereas classical and paradoxical low-flow, low-gradient AS are classified as D2 and D3 stages, respectively (**Figure 1**). These guidelines propose a class I recommendation for AVR in the D1 stage and a class IIa recommendation in the D2 and D3 stages if the presence of severe stenosis is confirmed and the patient is symptomatic (**Figure 1**). Normal-flow (stroke volume index >35 ml/m^2), low-gradient AS with preserved LVEF is another frequent type of low-gradient AS that is not addressed in the current guidelines and for which the therapeutic management remains unclear (**Figure 1**) (2).

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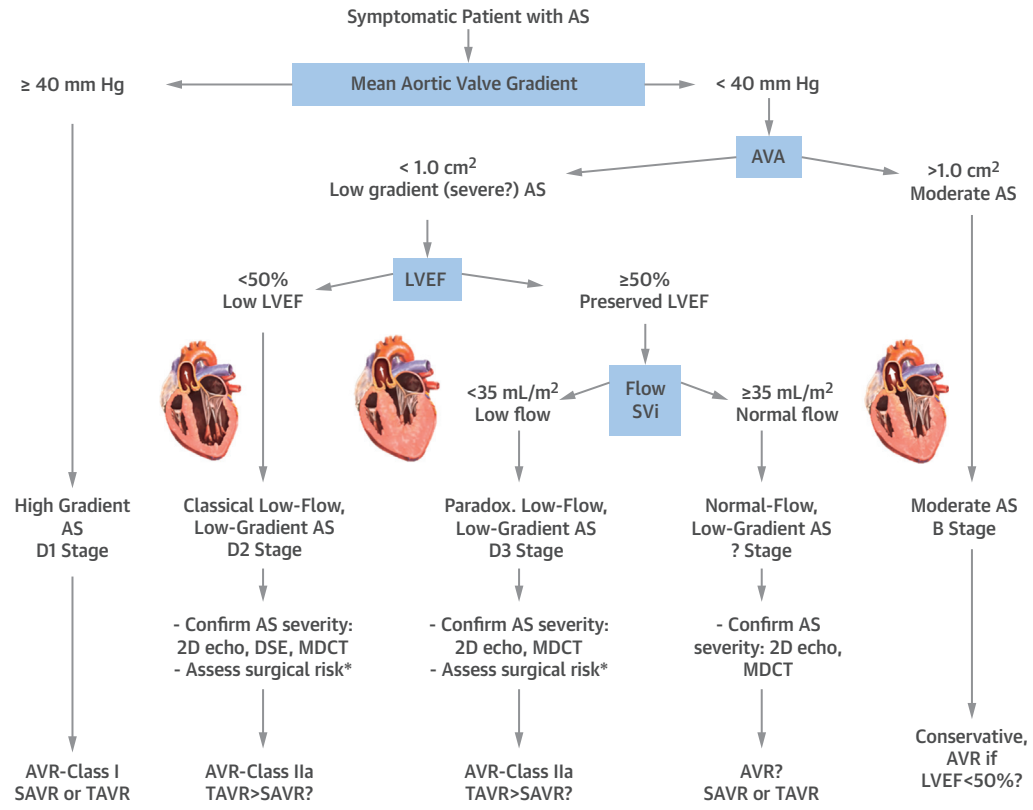
FIGURE 1 Algorithm for the Diagnosis and Management of the Different Types of LVEF/Flow/Gradient AS



*Assess surgical risk by: 1) using the algorithm proposed by American College of Cardiology/American Heart Association guidelines; and 2) considering additional risk markers specific to the AS population including gradient, stroke volume index, and flow reserve. ? = statements that are unknown or are still hypothetical and will need to be confirmed by future studies. AS = aortic stenosis; AVA = aortic valve area; AVR = aortic valve replacement; 2D echo = assessment of aortic valve morphology and motion by 2D transthoracic or transesophageal echocardiography; DSE = dobutamine stress echocardiography; LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography; Paradox. = paradoxical; SVi = stroke volume index; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

In this issue of the *Journal*, Baron et al. (5) report the results of an elegant study of a large series of patients from the Transcatheter Valve Therapy (TVT) Registry, in which they analyzed the impact of gradient and LVEF on 1-year outcomes following

SEE PAGE 2349

transcatheter AVR (TAVR). The main findings of this study are: 1) both low-gradient (<40 mm Hg) and low LVEF (<50%) are common in this population (52% and 49%, respectively) and are associated with increased risk of mortality and heart failure rehospitalization following procedure; and 2) after adjustment for other baseline risk factors, low gradient, but not LVEF, was independently associated with increased risk of 1-year outcomes. This study further emphasizes the importance of considering the gradient and LVEF in the risk stratification process of patients being candidates for TAVR.

Several previous studies including registries and post hoc analyses of randomized trials have reported that patients with low LVEF, low gradient, and/or low flow have worse outcomes following surgical AVR (SAVR) or TAVR (6–12). However, the main strength and incremental value of the present study (5) are that it includes a very large series (n = 11,292) of real-world patients undergoing TAVR. The study provides a contemporary and representative portrait of the impact of LVEF and gradient on outcomes in the TAVR population. In particular, this study is not subject to some selection biases inherent to the previous and ongoing TAVR trials including the PARTNER (Placement of Aortic Transcatheter Valves) trials, in which, for example, patients with very low LVEF (<20%) were excluded. However, as in the