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Discordant Low-Gradient Aortic Stenosis: Assessing the Valve and the Myocardium

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Low-gradient aortic stenosis (AS) is a challenging clinical condition characterized by an aortic valve area (AVA) less than 1 cm^2, which is consistent with severe AS but has a mean transvalvular pressure gradient lower than 40 mm Hg, which makes it consistent with nonsevere AS. The echocardiographic parameters of AS severity are discordant; thus, the level of AS severity remains undetermined. It is important in patients with discordant grading on echocardiography to use other imaging modalities to confirm the severity of AS and therefore the indication for aortic valve replacement (AVR). Three types of low-gradient AS are recognized:

- Classic low-flow, low-gradient AS, which is a form of AS with heart failure (HF) with reduced left ventricular ejection fraction (LVEF), categorized as stage D2 in the American guidelines.[1] This subtype is characterized by an LVEF lower than 50% and is generally associated with a low-flow state.
- Paradoxical low-flow, low-gradient AS, which is a form of AS with HF with preserved LVEF, categorized as stage D3 in the American guidelines. This subtype is characterized by a preserved LVEF (>50%) but nevertheless has a low-flow state, which is defined in the guidelines as having a stroke volume index less than 35 mL/m^2.
- Normal-flow, low-gradient AS, which is characterized by a preserved LVEF. It has a normal flow according to the stroke volume index but still has a discordance between the AVA and the mean pressure gradient.

Classic Low-Flow, Low-Gradient AS

The guidelines recommend AVR as a class I indication for patients with classic low-flow, low-gradient AS if the presence of true-severe AS can be confirmed on dobutamine stress echocardiography.[1,2] The European guidelines also recommend a computed tomography (CT) scan with calcium scoring to confirm AS severity in patients with limited or no flow reserve because dobutamine stress echocardiography is often nondiagnostic in this context. The European Association of Cardiovascular Imaging recommends the use of low-dose dobutamine stress echocardiography to increase the flow across the valve, and then differentiate true-severe AS from pseudosevere AS. The presence of a flow reserve (defined as an increase in stroke volume >20%) and a mean pressure gradient increase above 40 mm Hg with an AVA less than 1.0 cm^2 confirm true-severe AS and are an indication for AVR. A mean pressure gradient on stress echocardiographic scans below 40 mm Hg and AVA greater than 1.0 cm^2 are consistent with pseudosevere AS. In such cases, AVR is not indicated, and conservative management with close clinical and echocardiographic follow-up is recommended. If there is no flow reserve, which may occur in up to 50% of patients,[3] dobutamine stress echocardiography often remains nondiagnostic, and other modalities, such as CT scans, are recommended to confirm the severity of the stenosis. Noncontrast CT scans using the modified Agatston method can be used

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to quantitate the calcium burden on the aortic valve and therefore determine the anatomic severity of the stenosis. Different cutoff values for aortic valve calcium scores should be used in men (>2,000 Agatston units) vs women (>1,200 Agatston units) to confirm the presence of severe AS.

A French multicenter study has reported that patients with classic low-flow, low-gradient AS without flow reserve on dobutamine stress echocardiography have a high operative risk with surgical AVR.[4] Nevertheless, their long-term survival was better with surgery than with medical management. Conversely, in the TOPAS-TAVI registry, outcomes among patients with classic low-flow, low-gradient AS and no flow reserve following transcatheter AVR (TAVR) were as good as outcomes among patients with flow reserve with regard to 1-year mortality rates, improvement in LVEF, and functional status.[5] A study by Jean and colleagues[6] revealed that outcomes among patients with pseudosevere (ie, moderate) AS and systolic HF are poor on medical management, but outcomes among patients treated by AVR during follow-up are as good as those for a group of patients matched for age, sex, and LVEF with systolic HF and no AS. In a recent study by Ludwig et al,[7] patients with classic low-flow, low-gradient AS and pseudosevere AS confirmed by CT aortic valve calcium scoring had better outcomes with TAVR than with medical management. These findings support the concept that what is considered moderate AS for a good ventricle with preserved systolic function may actually be severe for a depressed ventricle. This concept led to the design of the TAVR-UNLOAD trial, in which 300 patients with moderate AS, systolic HF, and optimized medical therapy have been randomly assigned to TAVR or to continued medical therapy. The PROGRESS trial, in which patients with moderate AS and symptoms of cardiac damage or dysfunction have been randomly assigned to TAVR or clinical surveillance, is ongoing.

Paradoxical Low-Flow, Low-Gradient AS

The American guidelines recommend AVR with a class I indication in symptomatic patients with paradoxical low-flow, low-gradient AS for whom AS is the most likely cause of their symptoms.[1] The European guidelines also recommend AVR for these patients but with a class IIa indication.[2] Both guidelines insist that it is important to confirm the presence of true-severe AS in these patients,

Abbreviations and Acronyms

AS	aortic stenosis
AVA	aortic valve area
AVR	aortic valve replacement
CT	computed tomography
HF	heart failure
LVEF	left ventricular ejection fraction
TAVR	transcatheter aortic valve replacement

and CT aortic valve calcium scoring is recommended (class IIa) for this purpose. In the PARTNER 2 trial and registry, outcomes among patients with paradoxical low-flow, low-gradient AS or with normal-flow, low-gradient AS were as good as outcomes among patients with high-gradient severe AS, whereas patients with classic low-flow, low-gradient AS had lower rates of survival following AVR.[8] In the TOPAS registry, which included patients with classic and paradoxical low-flow, low-gradient AS, transfemoral TAVR was associated with better outcomes than surgical AVR or alternative-access TAVR.[9] Furthermore, outcomes were better with AVR than with conservative management in patients with low-flow, low-gradient severe AS.

Management of Low-Flow, Low-Gradient AS

In summary, the guidelines recommend the following approach to managing low-gradient AS. The first step is to confirm the validity of a patient's echocardiographic measurements. The second step is to define the LVEF/flow status and perform additional imaging to confirm the severity of the AS and the indication for AVR. In the presence of classic low-flow, low-gradient AS with reduced LVEF, the guidelines first recommend performing low-dose dobutamine stress echocardiography to differentiate true-severe from pseudosevere AS. If the dobutamine stress echocardiographic scan is inconclusive, the guidelines then recommend performing CT calcium scoring. In patients with paradoxical low-flow, low-gradient AS with preserved LVEF, dobutamine stress echocardiography is not the optimal test; instead, the guidelines recommend using CT calcium scoring to confirm the severity of the AS. For patients with normal-flow, low-gradient AS, the European guidelines suggest that the stenosis is unlikely to be severe; however, several studies and meta-analyses have shown that a substantial proportion of these

patients actually have true-severe AS and may benefit from AVR.[10,11] In symptomatic patients with normal-flow, low-gradient AS, it may therefore also be useful to perform a CT calcium score to confirm the severity of the stenosis and the need for AVR. The third step in the management of low-gradient AS is to determine the optimal type of AVR. Transfemoral TAVR may be preferred to surgical AVR in patients with low-flow, low-gradient AS, especially in patients with classic low-flow, low-gradient AS with no flow reserve. In patients with normal-flow, low-gradient AS, surgical AVR or TAVR can be used depending on surgical risk as well as the patient's age and preferences.

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