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Review Article

Moderate Aortic Stenosis With Cardiac Damage: A New Type of Severe Aortic Stenosis

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ABSTRACT

The clinical implications of severe aortic stenosis have been well established. Understanding of moderate aortic stenosis, however, continues to evolve. Athough moderate aortic stenosis may be less clinically impactful in patients with normal ventricular function, it may carry prognostic significance in those patients with a ventricle exhibiting signs of cardiac damage. Moderate aortic stenosis in the presence of cardiac damage or dysfunction may be prognostically comparable to that of severe aortic stenosis. Extravalvular risk parameters can inform aortic stenosis risk stratification. Three ongoing trials seek to evaluate transcatheter aortic valve assessment in patients with moderate aortic stenosis and signs of cardiac damage or left ventricular dysfunction.

ABBREVIATIONS

AVR, aortic valve replacement; LV, left ventricular; LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement.

Introduction

Clinical or subclinical cardiac damage and dysfunction in the presence of aortic stenosis is a prognostically important clinical entity. Here, we review the significance of moderate aortic stenosis in the presence of cardiac structural or functional damage, the relevant pathophysiologic mechanisms underlying this significance, and the ongoing efforts to understand the role of aortic valve intervention in these patients (Graphic Abstract).

Heart Failure and Aortic Stenosis

Heart failure remains one of the leading causes of hospitalization worldwide.[1] Despite progressive advances in medical and interventional therapies, the overall prognosis for patients with heart failure is quite poor, with estimated 5-year mortality rates as high as 75%.[2] In parallel, aortic stenosis is the most common valvulopathy in the developed world.[3,4] Coexistence of aortic stenosis and heart failure is not infrequent and is associated with worse outcomes.[5]

Adjudicating the cause of left ventricular (LV) dysfunction in the presence of valve disease can be complicated by concomitant cardiac and noncardiac comorbidities such as coronary artery disease or hypertension. The hemodynamic effect of aortic stenosis is determined by the LV hemodynamic load induced by the combination of aortic stenosis severity and systemic vascular resistance balanced against the intrinsic contractile capacity of the LV to overcome this load at rest or with exertion. Elevated valvulo-arterial impedance (a measure of the combined valve and arterial component of LV afterload) incorporates the increased valvular load and the increased systemic vascular resistance observed in aortic stenosis patients due to decreased vascular compliance (a function of the same systemic atherosclerotic process that is also driving the development of aortic stenosis). Valvulo-arterial impedance has been tied to outcomes in patients with aortic stenosis and may be a more accurate assessment of overall LV load and risk.[6–8]

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The optimal hemodynamic state for any given LV consists of a balance between the contractile capacity of the LV and the valvulo-arterial impedance or afterload of that LV. In patients with depressed LV function, the LV capacity to overcome the hemodynamic load may be impaired.[9,10] Thus, moderate aortic stenosis in the presence of impaired ventricular function may share more pathophysiologic parallels with severe aortic stenosis in the presence of normal LV function than it does with moderate aortic stenosis in the presence of preserved LV function.

Traditional medical therapy, which forms the mainstay of heart failure management, targets reduction in systemic vascular resistance through neurohormonal modulation.[11] These pharmacotherapies do not modulate the valvular component of increased LV afterload. Aortic valve replacement (AVR) may, however, prove to be an effective therapy for modulating the valvular contribution to increased valvulo-arterial impedance. At present, however, there is no indication for AVR in patients with moderate aortic stenosis and heart failure unless there is a concomitant indication for cardiac surgery.[12] Nonetheless, current clinical trials seek to test the hypothesis that, in the presence of systolic or diastolic cardiac dysfunction, a combined approach to reduce LV afterload with AVR combined with medical therapy leads to improved clinical outcomes.

Risk Stratification for Moderate Aortic Stenosis

Aortic stenosis is a progressive disease that ought to be considered in conjunction with cardiac and noncardiac adaptations that inform outcomes.[13] It is known that aortic stenosis begins to drive LV diastolic dysfunction and associated symptoms prior to the manifestation of systolic dysfunction.[14] While concentric LV hypertrophy is an early adaptive mechanism to the increased afterload of aortic stenosis, increasing LV systolic wall stress leads to LV dysfunction, LV fibrosis, and potentially irreversible myocardial damage.[15] Assessment of aortic stenosis patients with cardiac magnetic resonance imaging has demonstrated that myocardial fibrosis is found in patients with moderate aortic stenosis.[16] AVR may not always lead to LV recovery, especially in patients with pre-existing myocardial fibrosis, further underscoring the importance of early identification of at-risk patients prior to the development of irreversible changes.[17]

An aortic stenosis staging classification based on the extent of cardiac damage was first proposed and validated in severe-symptomatic aortic stenosis patients at high surgical risk undergoing AVR.[18] The proposed classification schema incorporates extravalvular cardiac changes to help improve aortic stenosis prognostication. Patients with aortic stenosis without extravalvular cardiac damage are considered stage 0, with the presence of LV damage as stage 1, atrial or mitral valve damage as stage 2, pulmonary vasculature or tricuspid damage as stage 3, or right ventricular damage as stage 4.[18] Application of this staging schema to a moderate aortic stenosis population demonstrates a stepwise increase in risk of death with increasing stages further validating the need to incorporate extra-valvular changes in the risk stratification of moderate aortic stenosis.[19,20] Importantly, cardiac and noncardiac comorbidities, such as the higher prevalence of concomitant coronary artery disease observed in patients or the presence of systemic disease such as amyloidosis, may additionally influence outcomes in patients with moderate aortic stenosis.[21]

Outcomes in Moderate Aortic Stenosis

Risk stratification of aortic stenosis merits a complex integration of aortic valve stenosis severity with cardiac and extracardiac comorbidities. A clear stepwise increase in mortality exists with increasing aortic stenosis severity.[22] Assessment of aortic valve stenosis is influenced, however, by the real-world challenges of adequate grading of aortic stenosis severity coupled with the often discordant findings of echocardiographic data. Discordant aortic stenosis (i.e., severe aortic stenosis by aortic valve area but moderate by gradient or moderate by aortic valve area but mild by gradient) is an important clinical entity nonetheless associated with worse prognosis that highlights the challenges of quantifying aortic stenosis.[23]

Patients with moderate aortic stenosis, in particular, have impaired survival and increased heart failure hospitalizations, with 5-year survival rates as low as 52%.[24,25] This, in part, may reflect the increased risk of accelerated progression to severe aortic stenosis in these patients. Nonetheless, the presence of symptoms has been associated with an increased risk of death purely in the presence of moderate aortic stenosis.[25,26] This suggests an independent risk of moderate aortic stenosis. Decreased survival has been observed in moderate aortic stenosis patients with low-normal LV function or symptomatic functional class suggesting that moderate aortic stenosis is clinically relevant prior to overt LV systolic dysfunction.[21] Noninvasive markers of subclinical LV dysfunction, such as global longitudinal strain or diastolic assessment, corroborate this idea and suggest promise in early identification of at-risk patients with moderate aortic stenosis.[27,28]

The risk of death is especially increased in those patients with moderate aortic stenosis and reduced LV function, with nearly a threefold increased risk of death in patients with moderate aortic stenosis and reduced LV function compared to patients with reduced LV function and no aortic stenosis.[4,25,29] In a propensity-matched cohort of heart failure with reduced ejection fraction patients with and without moderate aortic stenosis, aortic valve intervention appears to attenuate the risk of aortic stenosis to nearly that of matched patients without aortic stenosis.[4] Improvement in survival has been observed in both transcatheter and surgical aortic valve replacement in patients with impaired LV function and moderate aortic stenosis.[4,30] These observational findings further underscore the need for randomized data to inform clinical practice in moderate aortic stenosis with clinical or subclinical signs of cardiac damage.

Aortic Valve Replacement in Moderate Aortic Stenosis

There is presently no indication for aortic valve intervention in patients with moderate aortic stenosis, even in the presence of heart failure, unless the patient is undergoing cardiac surgery for other indications. Three ongoing clinical trials seek to assess the clinical benefit of early transcatheter aortic valve replacement (TAVR) in symptomatic patients with moderate aortic stenosis and systolic LV dysfunction (TAVR UNLOAD) or other signs of cardiac damage (EXPAND TAVR II-self-expanding valve platform; PROGRESS-balloon expandable valve platform, Table 1).

The Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial seeks to compare the efficacy and safety of balloon expandable transcatheter aortic valve replacement (TAVR) in addition to optimal medical therapy compared to optimal medical therapy alone in patients with moderate aortic stenosis (defined as mean transaortic gradient $\geq$20 mmHg and $<$40 mmHg and an aortic valve area $>$1.0 cm^2 and $\leq$1.5 cm^2 at rest or after dobutamine stress echocardiography), reduced ejection fraction (left ventricular ejection fraction [LVEF] $<$50%), and New York Heart Association Class II or greater symptoms (Table 1). Symptomatic heart failure is confirmed by an elevated N-terminal pro b-type natriuretic peptide or b-type natriuretic peptide ($>$1500 pg/mL or $>$400 pg/mL, respectively) or a hospitalization due to heart failure within the last year. If transthoracic echocardiography assessment is discordant (i.e., mean aortic valve gradient $\geq$20 mmHg and $<$40 mmHg and AVA $\leq$1.0 cm^2 at rest), low dose dobutamine stress echocardiography is performed to distinguish among patients with true severe aortic stenosis. The primary end point at 2 years is the hierarchical occurrence of all-cause death, disabling stroke, hospitalizations related to heart failure, symptomatic aortic valve disease or nondisabling stroke, and change in the Kansas City Cardiomyopathy Questionnaire at 1 year. Notably, patients with LVEF $<$20%, patients in need of coronary revascularization, those with heart failure hospitalization within 2 weeks of randomization, and

Table 1
Current randomized clinical trials of early transcatheter aortic valve replacement (TAVR) for the treatment of moderate aortic stenosis with symptoms or cardiac damage

	TAVR UNLOAD (n = 178)	EXPAND TAVR II (n = 650)	PROGRESS (n = 750)
Moderate aortic stenosis	**1. AVA (Rest)**>1.0 cm^2 and ≤1.5 cm^2 *OR* **2. AVA (DSE)**>1.0 cm^2 when low-flow is suspected	**1. AVA**>1.0 cm^2 to <1.5 cm^2 *AND* **2. V_{Peak}**≥3.0m/s to <4.0 m/s *AND* **3. MG**≥20 to <40 mmHg	**1. AVA**>1.0 cm^2 and ≤1.5 cm^2 *OR* **Indexed AVA**>0.6 and ≤0.9 cm^2/m^2 (>0.5 and ≤0.8 cm^2/m^2 if BMI≥30 kg/m^2 *AND* **2. V_{Peak}**≥3.0m/s to <4.0 m/s *OR* **3. MG**≥20 to <40 mmHg If only one of the 2 criteria above is met on rest TTE and: i) LVEF <50%: both criteria 1 and 2 are met on DSE; ii) LVEF≥50%: CT calcium score in <1200 AU in women and <2000 AU in men.
Symptoms	NYHA II or greater	One of: NYHA II or greater 6MWT<300 meters <85% of age-sex predicted METs on exercise tolerance testing	NYHA II or greater
Risk features	LVEF <50% at rest on at least 1 mo of GDMT	Symptoms *AND one of the following:* HF hospitalization within 1 calendar year NT-proBNP≥600 pg/mL (or BNP 80 pg/mL) LVEF<60% GL ≤-15% E/e'≥14 or≥Grade 2 diastolic dysfunction Stroke volume index <35 mL/m^2	Symptoms *OR one of:* LVEF<60% Stroke volume index <35 mL/m^2 ≥Grade 2 diastolic dysfunction Atrial fibrillation NT-proBNP>3x normal Elevated calcium score
Primary endpoint	Hierarchical occurrence of: all-cause death; disabling stroke; hospitalizations related to HF, symptomatic aortic valve disease or nondisabling stroke, or clinically significant worsening of HF; change in KCCQ	Composite rate of all-cause mortality, heart failure hospitalization or event, or medical instability leading to aortic valve replacement or re-intervention	Composite rate of death, stroke, and unplanned cardiovascular hospitalization at 2 y

Abbreviations: 6MWT, 6-Minute Walk Test; AVA, aortic valve area; BMI, body mass index; BNP, b-type natriuretic peptide; CT, computed tomography; DSE, dobutamine stress echocardiography; GDMT, goal-directed medical therapy; GLS, global longitudinal strain; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MG, mean aortic valve gradient; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; TAVR, transcatheter aortic valve replacement; TAVR UNLOAD, Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure; TTE, transthoracic echocardiography; V_{Peak}, peak aortic velocity.

bicuspid aortic valves were excluded.[31] The trial is sponsored by the Cardiovascular Research Foundation (New York, NY).

The EXPAND TAVR II pivotal trial seeks to assess the safety and effectiveness of a self-expanding valve platform in symptomatic patients with moderate aortic stenosis and evidence of cardiac damage (Table 1). Moderate aortic stenosis included an expanded definition defined by peak velocity, mean gradient AND aortic valve area: i.) maximum aortic velocity ≥3.0 m/sec and <4.0 m/sec; ii.) mean aortic gradient ≥20.0 mmHg and <40.0 mmHg; and iii.) aortic valve area >1.0 cm^2 and <1.5 cm^2. In addition, patients were required to have evidence of symptoms, LVEF >20%, and one of: heart failure hospitalization within 1 calendar year; N-terminal pro b-type natriuretic peptide ≥600 pg/mL (or b-type natriuretic peptide 80 pg/ml); global longitudinal strain ≤15%; or E/e' (average of medial and lateral velocities) ≥ 14.0. Notably, patients with LVEF ≤20%, Sievers 0 or 2 bicuspid aortic valves, and those with coronary artery disease are among those patients excluded. Follow-up is extended to 2 years with the composite outcome of all-cause mortality, heart failure hospitalization, or need for aortic valve replacement or reintervention measured. The EXPAND TAVR II trial is sponsored by Medtronic Inc. (Minneapolis, MN).

The PROGRESS Trial (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement) is assessing a balloon expandable TAVR platform in symptomatic patients with moderate aortic stenosis and signs of cardiac damage. Moderate aortic stenosis is defined as an aortic valve area of >1.0 cm^2 and ≤1.5 cm^2 AND either a peak velocity ≥3.0 m/s to <4.0 m/s OR a mean gradient ≥20 to <40 mmHg. In case of discordant grading at rest echocardiography, low-dose dobutamine stress echocardiography (if LVEF <50%) or computed tomography calcium scoring (if LVEF ≥50%) can be used. Patients are required to have New York Heart Association II or greater symptoms or have one of the following risk factors: LVEF <60%, Grade 2 or greater diastolic dysfunction, stroke volume index <35 mL/m^2, persistent atrial fibrillation or a paroxysmal episode in the preceding 6 months, NT-proBNP >3x normal, or an elevated computed tomography aortic valve calcium score. The primary endpoint is the composite of death, stroke, and unplanned cardiovascular hospitalizations at 2 years. Patients with an LVEF <20% are excluded. The PROGRESS trial is sponsored by Edwards Lifesciences (Irvine, CA).

Conclusions

Moderate aortic stenosis in the presence of clinical or subclinical cardiac damage or dysfunction shares prognostic similarities to severe aortic stenosis. Moderate aortic stenosis may be well tolerated by a normal ventricle but poorly tolerated by a ventricle exhibiting signs of cardiac damage. Extra-valvular risk parameters such as LV function or functional class are important aspects of aortic stenosis risk stratification. Three presently ongoing prospective randomized trials seek to evaluate the clinical benefit of transcatheter aortic valve assessment in patients with moderate aortic stenosis and signs of cardiac damage or LV dysfunction.

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