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EDITORIAL COMMENT

Aortic Stenosis

The Emperor's New Clothes*

Mani A. Vannan, MBBS,[a] Philippe Pibarot, DVM,[b] Patrizio Lancellotti, MD, PhD[c]

Survival in symptomatic severe aortic stenosis (AS) is dismal without either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement. It is also now well recognized that symptoms in individuals with severe AS may be unreliable and there is increasing evidence that, even in cases of truly asymptomatic severe AS, there are factors which constitute very severe AS (1). The 2-year event-free survival of untreated asymptomatic very severe AS is ~40% (compared to ~70% for asymptomatic severe AS). Therefore, those patients with low surgical risk with very severe AS may benefit from AVR, even in the absence of symptoms. There are large randomized studies (AVATAR [Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis], EVoLVeD [Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe AS], ESTIMATE [Early Surgery for Patients with Asymptomatic Aortic Stenosis], and EARLY-TAVR [Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis]) underway to assess the efficacy and safety of early TAVR versus conservative management in cases of asymptomatic severe AS, the results of which will perhaps help us move away from relying only on symptoms prior to triggering AVR in severe AS (2).

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In this issue of the *Journal*, Strange et al. (3) provide short- and long-term clinical outcome findings in 241,303, individuals identified from the National Echocardiography Data of Australia (NEDA) as having either no AS, mild AS, moderate or severe AS. Aortic valve maximum velocity (Vmax) and mean gradient (MG) were used to categorize these patients, except for those with a stroke volume index (SVi) <35 ml/m^2 when calculated aortic valve area (AVA) was used to classify AS. Patients with no AS (n = 215,476; MG: <10 mm Hg; Vmax: <2.0 m/s) and those with mild AS (n = 16,129; MG: 10 to 20 mm Hg; Vmax: 2.0 to 3.0 m/s) had similar survival rates at 1 and 5 years. Patients with high- or low-gradient severe AS (n = 6,383; MG: >40 mm Hg; Vmax: >4.0 m/s; or AVA: <1.0 cm^2) had a 3-fold increase in mortality over the same period, which confirms what is known. However, the most intriguing finding was that the mortality rate in patients with moderate AS (n = 3,315; Vmax: 3.0 to 4.0 m/s; and MG: 20 to 30 mm Hg) was similar to that in those with severe AS. In fact, the data suggest that a Vmax of >3 m/s or a MG of >20 mm Hg was the inflection point at which there was a 2-fold increase in mortality compared to that in patients with mild AS. This was true even when sex, age, SVi, left ventricle ejection fraction (LVEF), and the presence of aortic regurgitation were taken into consideration.

Thus, is moderate AS not a benign stage in the evolution of the disease as the conventional wisdom tells us? The answer is as complex as it is unclear, but it would be a folly to dismiss these provocative findings as mere technical errors in the Doppler echocardiographic data. There is no question that suboptimal Doppler echocardiographic in AS is often the source of inconsistent grading of the severity of AS. However,

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From the [a]Marcus Heart Valve Center, Piedmont Heart Institute, Atlanta, Georgia; [b]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Ville de Québec, Québec, Canada; and the [c]CHU Sart Tilman, University of Liège, Liege, Belgium. Dr. Pibarot has received funding from Edwards Lifesciences and Medtronic for echo corelab analyses and in vitro studies in the field of aortic valve replacement, with no personal compensation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

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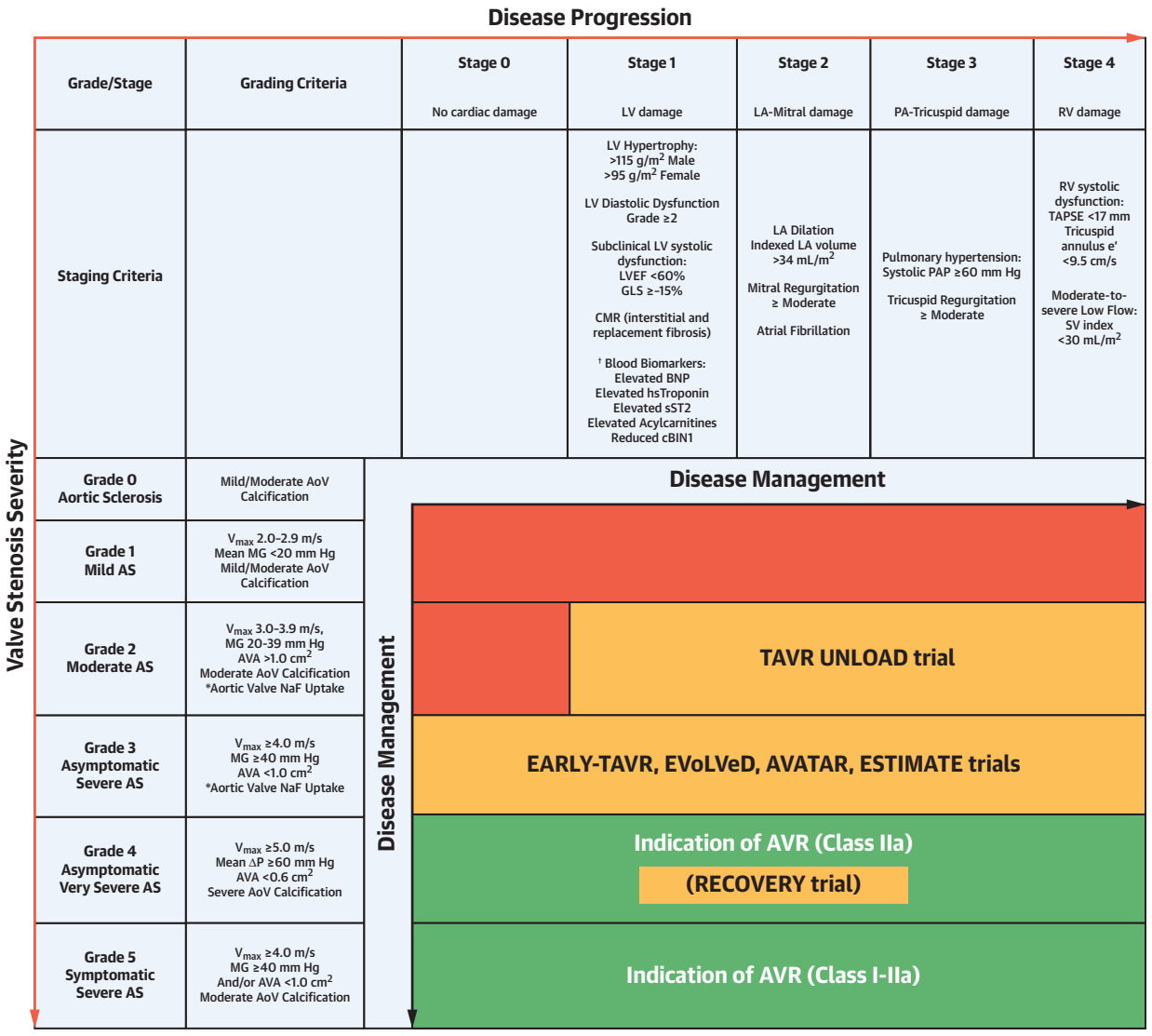
FIGURE 1 Schematic Connects Valve Lesion Severity to Disease Stage and Progression, Both of Which Influence Timing and the Need for Intervention



Red indicates conservative (follow-up) management. **Yellow** indicates no evidence yet for intervention, but ongoing trials will be instructive. **Green** represents current guideline-based indications for intervention in AS. *PET imaging. †BNP, myocardial stretch/volume status; troponin, myocardial injury; soluble ST2, myocardial remodeling; acylcarnitines, myocardial metabolic distress; cBIN1, cardio myocyte remodeling. AoV = aortic valve; AS = aortic stenosis; AVATAR = Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; AVR = aortic valve replacement; BNP = B-type natriuretic peptide; cBIn1 = cardiac bridging integrator 1; EARLY-TAVR = Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis; ESTIMATE = Early Surgery for Patients with Asymptomatic Aortic Stenosis; EVoLVeD = Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe AS; GLS = global longitudinal strain; Lp (a) = lipoprotein (a); LV = left ventricle; LVEF = left ventricle ejection fraction; MG = mean gradient; PA = pulmonary artery; PAP = pulmonary artery pressure; PET = positron emission tomography; RECOVERY = Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis; sST2 = soluble suppression of tumorigenicity-2; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion; TAVR UNLOAD = Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure; V_{max} = aortic valve maximum velocity.

the authors of the NEDA data recognize and acknowledge this. They have used Doppler velocity data for the most part and resorted to AVA, which involves measurement of left ventricular outflow tract diameter, the most common source of error in computation of AVA only when SVi was reduced. Also, they used dimensionless index (DI) to analyze the data and came to the same conclusion: patients

with DI 0.25 to 0.30 (moderate AS) demonstrated short- and long-term event dates similar to those with DI <0.25 (severe AS). Then there are limitations of observational data such as the lack of information about comorbid factors, which may have influenced the outcomes, or that many individuals with moderate AS might have progressed to severe AS since their last echocardiogram. Notwithstanding these limitations, the observation that moderate AS is not necessarily a benign condition has been made before. Chizner et al. (4) showed that 6 of the 10 patients with cardiac catheterization determined to have moderate AS (AVA: 0.71 to 1.09 cm^2) and peak aortic valve gradient <70 mm Hg died within 9 months after the diagnosis. Data from the study by Kennedy et al. (5) showed that, in those with AVA 0.7 to 1.2 cm^2 (classified as moderate AS), the 4-year event-free survival was only 59%, even in the absence of symptoms (or minimally symptomatic) or dysfunction. The presence of symptoms or LVEF <50% in these patients worsened the outcome. Also, the presence of coronary artery disease had no demonstrable effect on AS-related events. It is possible that some of the patients in these 2 studies had severe AS based on the current definition based on AVA, which is <1 cm^2. However, at normal flow rates, a MG of 40 mm Hg (one of the indices for severe AS) is usually reached only when the AVA is reduced to ~0.8 cm^2, which is similar to the threshold the authors used to differentiate moderate from severe AS in these 2 studies. There are also more contemporary data (6) which all confirm these findings in moderate AS. More recently, data from Van Gils et al. (7). and Lancellotti et al. (8) showed higher adverse event rates in moderate AS (using the current Doppler echocardiographic definition) than in those with LVEF <50% and an age-matched population with mild AS, respectively.

How do we interpret and what are the implications of these data for moderate AS? These data may prompt reconsideration of the current time-honored approach of classifying AS as mild, moderate, and severe using Doppler echocardiographic data. This approach by its nature implies that the assessment of the degree of AS is relevant to that single point of assessment of the valve and that Doppler hemodynamics are by themselves not sufficient to fully characterize the disease severity. The under-recognition and undertreatment of severe AS, which is said to be as high as ~70% in some estimates, may in fact be due in no small measure to over-reliance on such firm categorization of AS based on Doppler echocardiographic data alone. The challenge is to consider a less dogmatic approach by staging the disease instead of classifying the disease based solely on valve hemodynamics. Recent descriptions of staging AS using multiple cardiac and noncardiac factors are instructive and thought provoking (9,10). The composite evaluation of risk using such a staging method puts the focus on the *disease* rather than on isolated factors. This may move the needle toward timely and earlier intervention in AS to potentially fully reverse the adverse cardiac effects of AS after intervention (8). Integration of myocardial structural changes (fibrosis and scar assessment by cardiac magnetic resonance imaging) and more sensitive indices of myocardial dysfunction (strain measurements using speckle tracking echocardiography) in the staging of AS will further refine the utility of these schemes. Advances in the identification of biomarkers which signal not only myocardial injury or stress (troponin, N-terminal pro-B-type natriuretic peptide concentrations) (2) but metabolomic markers (11), which indicate myocardial metabolic distress, will surely aid in further refining the staging of the disease. Finally, biomarkers such as lipoprotein(a) and oxidized phospholipids (OxPL) indicate disease activity in the valve. These are exciting new frontiers, which not only allow staging the disease but can predict progression (12). Furthermore, they provide a tool for surveillance and are potential treatment targets for slowing disease progression. When analyzed collectively, these findings raise the hypothesis that early AVR is beneficial in patients with moderate AS at an advanced stage of cardiac damage and high risk of rapid progression of AS. This hypothesis is currently being tested in the TAVR-UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure) trial which compares TAVR with medical management in patients with moderate AS and systolic heart failure (2).

In summary, the complete characterization of AS includes *disease* severity, progression, and management, the emphasis being the *disease* not just the valve (**Figure 1**). TAVR is a ground-breaking advance in the treatment of AS, which is now applicable to patients with severe AS at low-risk for surgery. Therefore, it behooves us to open our eyes, ears, and minds and continue to make strides in the effective and timely management of the significant public health problem that is AS. It is worth remembering the words of C.S. Lewis: “What you see and what you hear depends a great deal on where you are standing” (13).

ADDRESS FOR CORRESPONDENCE: Dr. Mani A. Vannan, Piedmont Heart Institute, Marcus Heart Valve Center, 95 Collier Road, Suite 2065, Atlanta, Georgia 30309. E-mail: Mani.vannan@Piedmont.org. Twitter: @PiedmontHeart.

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