Editorial

Outcomes with moderate aortic stenosis and impaired left ventricular function: prelude to a randomized trial?

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The natural history of severe, symptomatic aortic stenosis (AS) has been well characterized, with most studies demonstrating a mortality rate of 50% at 2 years once patients develop symptoms of left ventricular (LV) systolic dysfunction (1,2). This precipitous decline in survival forms of the basis of current American Heart Association/American College of Cardiology class I recommendations for aortic valve replacement (AVR) in patients with: severe, symptomatic AS; asymptomatic patients with severe AS and a LV ejection fraction <50%; and patients with severe AS undergoing other cardiac surgery (3). However, AS is a progressive disease with an observed reduction in aortic valve area of approximately 0.1 cm^2 per year (4,5). As such, current guidelines also recommend AVR for patients with moderate AS undergoing other cardiac surgery (3). An extension of current guidelines thus follows—should AVR be considered for patients with moderate AS and impaired LV function?

This question is particularly relevant in the setting of growing rates of heart failure (HF) (6,7). In the United States, it has been projected that the prevalence of HF will increase by 46% with over 8 million individuals diagnosed with HF by 2030 (8). Once a diagnosis of HF is made, the 1- and 5-year mortality rates are estimated at 20% and 50%, respectively (9,10). As a decline in aortic valve area correlates with progressive LV dysfunction, studies have suggested that moderate AS may be associated with a reduction in long-term survival (4,11-13). The pathological basis for this correlation stems from the imbalance between increased LV hemodynamic load from valvular stenosis and the inability of the LV to overcome this load, which may be more pronounced in patients with impaired LV function (14). Capoulade and colleagues, for example, demonstrated that for every 0.1 cm^2 decrease in aortic valve area, the hazard ratio for all-cause mortality increased by 20% (15).

Several authors have sought to further quantify the natural history of moderate AS. A small study by Kennedy and colleagues examined patients identified with moderate AS at the time of cardiac catheterization and found the probability of remaining free of any complication of AS at 4 years to be 59%, with impaired LV function being a significant risk factor (16). Among elderly patients studied in the Helsinki Aging Study, authors observed a 35% cardiovascular-related mortality rate among patients aged 75–86 years old with moderate AS (17). Yechoor and colleagues examined a contemporary cohort of Veterans Administration patients who presented with moderate AS and found that at a mean follow-up of 22 months, 30% of patients went on to valve replacement surgery and 61% died, with an event-free survival rate of 24% at 3 years (18). Moreover, Samad and colleagues, in a large contemporary cohort, demonstrated that among patients with moderate AS, AVR was associated with a 5-year reduction in mortality of 32% (19).

In their current analysis, van Gils and colleagues

advance the knowledge base for outcomes with moderate AS by studying the natural history of patients diagnosed with moderate AS and impaired LV function using echocardiography databases from 4 academic medical centers (20). Patients were considered to have moderate AS if the aortic valve area was between 1.0 and 1.5 cm^2 and the peak aortic jet velocity was between 2 and 4 m/s at rest or after dobutamine stress echocardiography. Patients were considered to have LV systolic dysfunction if the left ventricular ejection fraction (LVEF) was <50%. The primary endpoint of the analysis was a composite of all-cause mortality, AVR, and HF hospitalization. At 4 years, the event rate for the primary composite endpoint was 61%, with 24% of patients reaching the primary endpoint by 1 year. When the composite endpoint was further analyzed, the authors observed at 4 years of follow-up that all-cause mortality occurred in 36% of patients, HF hospitalization in 27%, and AVR in 24%. Risk factors for achieving the primary endpoint included male sex, New York Heart Association class III or IV, and higher transaortic Vmax on index echocardiogram.

While the results of van Gils and colleagues add to a growing body of evidence demonstrating long-term adverse events among patients with moderate AS and impaired LV function, the results must be understood in the context of several limitations. First, the analysis is both retrospective and multinational and therefore includes a heterogenous population of patients with both varying HF medical management as well as varying HF etiologies. The most common etiology for HF in the US is ischemic cardiomyopathy yet only 16% of AVR patients underwent concomitant CABG. Second, while the authors used standard echocardiographic criteria for defining moderate AS, when aortic valve area index (AVAI) was calculated, 33% of patients in the study cohort had an AVAI <0.6 cm^2/m^2. Therefore, it is possible that a third of patients in the study were moderate to severe AS versus true moderate AS. This observation may, in part, explain the reason why 24% of patients reached the primary endpoint in 1 year. Third, surveillance intervals of echocardiographic imaging were not standardized in the study with a follow-up echocardiogram available in only 56% of patients. It is certainly possible that patients who failed to have follow-up echocardiograms did so because they were asymptomatic and had no perceived need to seek ongoing surveillance imaging. Data on these missing patients could have significantly altered the study findings. Fourth, 76% of patients in the analysis were symptomatic but it is unclear to what extent symptoms and LV dysfunction were truly due to AS. In the patients who underwent AVR therapy 63% underwent SAVR whereas 37% underwent TAVR. This relatively high proportion of TAVR may indicate heterogeneity in comorbid conditions that influence LV dysfunction and symptoms of HF such as underlying renal or pulmonary disease. Lastly, the decision-making process for timing and indications for AVR among the original study cohort are unclear. Among patients who underwent AVR and had a follow-up echocardiogram, there was no significant change in the LV ejection fraction, peak velocity, or mean gradient while aortic valve area decreased to a mean of 1.0 cm^2.

Based on the growing literature of retrospective analyses on the natural history of moderate AS, including the current study by van Gils and colleagues, one may ask—have we accumulated sufficient evidence to support a prospective, randomized trial of AVR for moderate AS? Despite the limitations of current retrospective data, the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial has been developed (21). TAVR UNLOAD will be a multicenter, randomized trial comparing the efficacy of TAVR plus optimal heart failure therapy (OHFT) *vs.* OHFT alone in patients with moderate AS and a reduced ejection fraction. The primary endpoint, assessed at 1 year, is a composite of death, disabling stroke, HF hospitalizations, symptomatic aortic valve disease or non-disabling stroke, and change in Kansas City Cardiomyopathy Questionnaire (KCCQ). The trial will enroll 600 patients and is powered to detect between an 8.2–11.5% difference in major adverse cardiac and cerebral events at 1 year. The rationale for TAVR UNLOAD is based on the assumption that for patients with moderate AS and impaired LV function, afterload reduction, achieved through TAVR, will be an effective means of reducing hemodynamic load and therefore improve long-term morbidity and mortality. If the results of TAVR UNLOAD are in favor of AVR, these findings would form the basis for a paradigm shift toward more aggressive management of moderate AS. However, there are several important considerations with such a trial.

The first major consideration is the timing of TAVR UNLOAD. The PARTNER 3 low-risk TAVR trial is still enrolling with results not expected for another 2 years (22). While we know that TAVR is non-inferior to surgical AVR (SAVR) with regard to death or disabling stroke in intermediate risk patients, we also know that TAVR is associated with higher rates of permanent pacemaker implantation and continue to await data on long-term valve durability (23). Even though 63% of patients who

required AVR in the study by van Gils and colleagues received SAVR, the TAVR UNLOAD trial only randomizes patients to transfemoral TAVR. Beyond the issue of timing with respect to TAVR versus SAVR, a broader question surrounds whether there is a significant evidence base to justify any intervention at all. Most retrospective studies that form the basis for TAVR UNLOAD lack data on etiology for impaired LV function, frequency of surveillance echocardiography, or cause of death. Prior to launching TAVR UNLOAD, it would have been interesting to develop a natural history study of patients with moderate AS and impaired LV function who had regular echocardiograms at 6-month intervals with OHFT. It is certainly possible that the observed mortality rate in previous retrospective analyses may be much lower in patients receiving optimal medical therapy and regular follow-up imaging. Such findings would suggest that what is really needed is closer surveillance and not earlier intervention. Any tissue valve implantation procedure is associated with peri-procedural risk and valve degeneration beginning at the time of implantation. From a methods standpoint, a third consideration involves the primary endpoint. With such a heterogeneous composite that includes death, stroke, HF hospitalizations, symptomatic aortic valve disease, and change in KCCQ, the findings of the study may be difficult to interpret. While the TAVR UNLOAD trial will employ an innovative, Finkelstein and Schoenfeld win ratio approach for analyzing the primary endpoint (24), it must be noted that the study, based on a heterogeneous composite endpoint, will not be powered to answer a simple question—does TAVR improve long-term survival in patients with moderate AS and impaired LV function. The final consideration deals with the health policy implications of a moderate AS TAVR trial. The cost-effectiveness of TAVR remains an area of continued investigation and the economic implications of potential FDA approval for TAVR among low-risk, severe AS patients is unclear (25). Further, rapid expansion of TAVR to a potentially much larger pool of moderate AS patients would have significant health policy implications and potentially prove to not be cost-effective compared to more aggressive echocardiographic surveillance imaging.

Conclusions

Moderate AS with impaired LV function represents an area in need of further scientific inquiry. Retrospective data suggest that such patients may be at increased risk of long-term mortality due to increased valvular hemodynamic load. However, current analyses are limited by many unknown factors that may affect the relationship between moderate AS and risk of death. Despite these limitations, the TAVR UNLOAD trial will soon assess the effectiveness of TAVR plus OHFT in patients with moderate AS and impaired LV function. As the field of transcatheter therapeutics rapidly expands, caution must be exercised in pace of new clinical trials. Do we have adequate natural history data to justify a trial, and are we solving a true medical problem or searching for broader indications for TAVR? The TAVR UNLOAD trial will provide important data on outcomes for patients with moderate AS and impaired LV function, how we then transform such findings into potentially new guidelines and balance the health economics of TAVR expansion will require significant thought.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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