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EDITORIAL COMMENT

Aortic Stenosis

Timing Is Everything*

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Aortic valve stenosis (AS) accounts for an increasing global burden of disease as lifespan increases. No medical therapy has been shown to slow AS progression, and the only effective treatment option thus far remains aortic valve replacement (AVR). Therefore, timing of replacement is critically important in the management of AS. The balance between the upfront risks of replacement and the long-term risks of delaying is dynamic and corresponds with advancements in surgical and transcatheter techniques. Morbidity and mortality associated with AVR have declined over the years, and transcatheter implantation has changed the landscape of valve replacement in high-risk patients with AS. The use of transcatheter aortic valve replacement (TAVR) has migrated to patients with increasingly lower risk with promising short- and medium-term outcomes.

Severe AS that causes symptoms or left ventricular ejection fraction (LVEF) <50% carries a poor prognosis and are established Class I indications for AVR, as are patients with severe AS undergoing cardiac surgery for separate indications. As the risks of intervention continually decrease, there is cumulative evidence in favor of early AVR in patients with asymptomatic AS who have rapid progression, significant hemodynamic consequences, or markers of early cardiac damage.[1] In the latter category, elevated B-natriuretic peptide and subtle decline in LVEF to low-normal range have been shown to be associated with poor survival.[2,3] Other signs such as myocardial fibrosis on cardiac magnetic resonance imaging and impaired left ventricular strain have been proposed as markers of poor prognosis, but it remains to be seen how these factors weigh into clinical decision-making about the timing of AVR.[4,5]

In this issue of *JACC: Advances*, Azavedo et al[6] reported on quantifying the survival loss associated with intervening too late using a multicenter database of 2,030 patients with high gradient AS enrolled between 2000 and 2020. They found that the proportion of patients undergoing AVR without Class I triggers increased steadily over the 2 decades. While operative mortality was similar between patients with and without Class I triggers, patients who underwent intervention without Class I triggers had better 10-year survival than patients with symptoms or LVEF <50%. They further showed that LVEF <60% regardless of symptoms had a 10-year survival penalty of nearly a year compared to patients with LVEF >60%, while AVR in asymptomatic patients with LVEF >60% achieved a prognosis comparable to the general population. Overall, their data suggested a role for even earlier intervention than already proposed in both American and European society guidelines.

It is difficult to rely solely on symptom occurrence as a trigger for intervention because symptoms are often subtle, subjective, and confounded by comorbidities. Additionally, as the authors showed, the occurrence of symptoms as a trigger for AVR reduced survival. The study benefited from a relatively large amount of longitudinal data and shed important insights into temporal trends in indications and outcomes of AVR, as well as the trajectory of intervention moving forward. However, there were inherent limitations to the retrospective nature of the study, including bias from unavailable or incomplete data surrounding indications for AVR and presence of symptoms. The mean age of the patients was 75 years.

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The findings may not be applicable to younger patients, who would be more burdened by the long-term complications of AVR. The role of exercise testing, biomarkers such as B-natriuretic peptide, and measures of myocardial performance such as strain were not adequately assessed.

The publication of this study is timely in the context of other recent data on the burden and treatment of AS. Généreux et al[7] recently demonstrated in the largest AS cohort to date that a disproportionately large number of patients with severe AS did not undergo AVR, suggesting underutilization of AVR. It is reasonable to believe that a significant number of these patients with severe AS had either unrecognized symptoms or early markers of poor prognosis and would have benefited from AVR. Patients with moderate AS, for whom the current standard of care is close observation, also appear to be at increased risk of cardiovascular events and mortality. While this may reflect under recognition of severe AS, prospective trials are underway to examine the role of early intervention in this population.[8]

Most of the data supporting early intervention that informs current practice are derived from patients who underwent surgical AVR. In the study by Azavedo et al, only about 10% of patients underwent TAVR, which is contrary to TAVR uptake in contemporary clinical practice. In the United States, TAVR volume has surpassed surgical AVR volume in 2019, and TAVR is now the predominant method of intervention.[8] The short-term outcomes of TAVR in asymptomatic or minimally symptomatic AS are promising,[9] and we eagerly await long-term data in this population. TAVR has permitted the treatment of AS in the elderly with multiple comorbidities, and in these patients, the long-term performance of TAVR on a 10-year scale may have limited relevance compared to that in younger patients. As TAVR is being performed in lower-risk patients, particularly younger patients, it is important to consider the implications of prosthetic valve degeneration, need for repeat intervention, and the ensuing impact on long-term outcomes even beyond 10 years. Continual re-evaluation of the timing of aortic valve intervention is paramount in view of our improving ability to accurately discern prognostically important AS and the greater number of intervention options available.

Decision-making in medicine is often biased toward improving present-day symptoms, and it can be difficult for patients to consider the future over a span of decades. Aortic stenosis, a progressive and indolent disease, needs to be considered in this timescale. Patients may be keen to defer AVR when they are asymptomatic, as they may be hesitant to undergo a procedure with an upfront morbidity cost. Practitioners may want to delay AVR until it is necessary to maximize the longevity of the prosthesis. A shared decision-making process is vital considering the age, lifestyle, and comorbidities of the patient.

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