

# The Changing Landscape of Treatment for Aortic Stenosis: Continuing to Push the Boundaries



There has been an ongoing evolution in our understanding and subsequent management of the patient with aortic stenosis (AS). Valvular AS presents a mechanical obstruction to ventricular ejection at the aortic valve level, worsens over time, and with the onset of symptoms there is a rapidly declining course resulting in progressive heart failure and death. The advent of surgical aortic valve replacement (SAVR) nearly 60 years ago has been lifesaving for many patients with symptomatic severe AS, restoring quality of life to those with severe limiting symptoms. However, there was the upfront risk of open-heart surgery as well as possible adverse long-term consequences of a valve prosthesis including valve thrombosis, valve degeneration, thromboembolic events, and infection. Many elderly frail patients with symptomatic severe AS were not surgical candidates, and were thus relegated to a life of decompensated heart failure and eventual demise.

## EMERGENCE OF TRANSCATHETER AORTIC VALVE REPLACEMENT

Over the past decade, remarkable advances in catheter-based technology to treat AS percutaneously have become available. Transcatheter aortic valve replacement (TAVR) was first studied in high-risk inoperable patients and resulted in dramatic reductions in mortality: one of the most impressive effect sizes in modern medicine with a number needed to treat of only four to save one life.<sup>1</sup> From the early days of TAVR, there have been continual improvements in the technique. Its safety and efficacy have now been compared to SAVR across the entire spectrum of patients, showing non-inferiority of TAVR even in low-risk patients. Thus, we now have in our treatment

armamentarium the well-accepted SAVR, but also a much less invasive procedure which can be applied not only to those who are at high risk for SAVR, but also to most other patients who would benefit from relief of the stenosis.

## CHANGING LANDSCAPE OF TREATMENT FOR SEVERE AS

The process guiding therapeutic decision-making in AS has continued to evolve rapidly. The initial concept was to offer SAVR only to those at the highest risk of adverse events, given the relatively high operative mortality and the adverse consequences of the older generation valve prostheses. Thus, patients with AS were followed until the onset of symptoms, and referred for surgery only when symptoms developed. However, as surgical outcomes improved and newer generation prostheses were developed, the threshold for operation was lowered. Select subsets of patients who had severe AS were identified as being at higher risk for adverse events, with SAVR subsequently offered for the asymptomatic patient who developed left ventricular systolic dysfunction (indicating that the pressure overload from the valve was overwhelming the ventricle), a positive exercise test (with a decrease in blood pressure during exercise) and those with “very severe” stenosis.<sup>2</sup>

Now that TAVR is firmly established as a safe, effective, and less-invasive treatment option for severe AS, there continue to be appropriate questions about whether our traditional conservative approach truly remains the optimal therapeutic strategy. There is accumulating evidence that AS induces pressure overload–related myocardial fibrosis that is only partially reversible with valve replacement.<sup>3</sup> Therefore, following

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intervention, many patients continue to have persistently abnormal hemodynamics and risk of heart failure despite a preserved ejection fraction.<sup>4,5</sup> Additionally, even with careful observation following the current criteria for SAVR, there are patients who die suddenly with severe asymptomatic AS.

### SUMMARY OF CURRENT STUDIES

On this background, two studies in this issue of the *Mayo Clinic Proceedings* have further enhanced our evolving understanding of intervention in AS, finding predictive parameters that have not been used by clinicians in the past. Ito et al<sup>6</sup> performed an analysis of the high-risk AS population that was randomized to TAVR or surgery, stratified by baseline myocardial pathology with a reduced ejection fraction or stroke volume. A low stroke volume was predictive of higher 1-year mortality, indicating that this measurement of ventricular function is important. Notably, it was the less severely ill patients with preserved ejection fraction and preserved stroke volume who showed greater incremental benefit of TAVR over SAVR. This suggests that TAVR may result in less myocardial damage than the more invasive SAVR, and it is possible that patients with the least amount of baseline myocardial remodeling may actually have the most to gain from the periprocedural myocardial preservation seen with TAVR. The other study by Sharma et al<sup>7</sup> used body mass index to risk stratify patients undergoing TAVR and showed that patients with a lower body mass index had increased mortality (the so-called “obesity paradox”). This most likely relates to the presence of greater frailty in this cohort which is a crucial factor in modern risk stratification for TAVR,<sup>8</sup> and in the past many of these patients likely would have been considered inoperable.

### FUTURE DIRECTIONS

As outlined in the two articles published in this issue of the *Mayo Clinic Proceedings*, there are emerging parameters to help predict outcome which are currently not used by clinicians in our algorithmic approach to determine timing of intervention. Our

national guidelines for management of patients with valvular heart disease have set thresholds for the definition of “severe” AS based upon outcome studies from large numbers of patients.<sup>2</sup> However, such population-derived summary estimates may not necessarily apply to every individual patient, as evidenced by the observation that some patients currently classified as only “moderate” AS still experience a poor outcome.<sup>9</sup> Stated differently, for any unique patient with AS, that individual’s definition of severe disease is the stenosis severity beyond which myocardial performance is adversely affected, and at which point intervention will improve outcomes. Pragmatically, identifying this prognostic transition point is challenging in some patients, and also continues to evolve as the risks of therapeutic intervention are dynamically changing such as with TAVR. This is an area where data scientists exploring predictive analytics from big data and machine learning approaches may provide further insight for the individual patient.<sup>10</sup> Given the very large population of patients now presenting with AS, both conventional and novel analytic strategies will be essential to help determine the optimal care for these patients.

Additionally, as our ability to safely relieve obstruction and prognosticate patients with AS continues to evolve, the onus critically falls on the primary care provider to screen and identify AS early. Careful attention to the physical examination for signs of AS is the most useful and cost-effective screening test. There still remain a number of patients who present with end-stage heart disease from long-standing AS who could have benefitted from earlier recognition and intervention. Caregivers should understand that there are now evolving indications for intervention as the risk:benefit ratio for intervention is continually changing. Decision-making for AS intervention is complex and spans the spectrum of the healthier asymptomatic patient where treatment is considered to prevent the adverse consequences of long standing pressure overload, as well as the frail elderly patient who was in the past

thought to be at too high a risk for conventional SAVR but now may be considered for TAVR. Given all the treatment options now available, appropriate screening for severe AS and referral to a heart team are the most important steps in the care of the increasingly complex AS patients being seen in modern clinical practice.

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**Potential Competing Interests:** The authors report no competing interests.

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