The Final Word: Current Strategies for the Lifetime Management of Patients with Aortic Valve Stenosis

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Aortic valve stenosis (AS) is the most common form of valvular heart disease in developed countries, with a prevalence that increases exponentially with advancing age.[1,2] Several etiologies, including congenital abnormalities (i.e. bicuspid aortic valve) and rheumatic heart disease, can lead to AS, although degenerative processes directly related to aging are the most common. The progressive fibrosis and calcification of the aortic valve obstruct blood flow from the left ventricle to the ascending aorta during systole. As a result of this decrease in cardiac output, patients complain of decreased exercise capacity that might progress to heart failure or even death if left untreated.

In addition to medical therapy, aortic valve replacement is often needed to limit disease progression, improve prognosis, and enhance the quality of life. Historically, surgical aortic valve replacement (SAVR) has been the mainstay therapy in most patients, while transcatheter aortic valve replacement (TAVR) has been limited to those at high risk for surgery. Iterations in TAVR technologies and bioprosthetic valves' design have expanded TAVR indications to patients across the spectrum of surgical risk. This editorial describes the pathophysiology and management strategies of AS, with a particular focus on the recent extension of TAVR to low-risk patients.

Pathophysiology of Aortic Valve Stenosis

Lipid deposition into intima cusps with subsequent oxidation constitutes the primary mechanism of pathogenesis of degenerative AS. This process triggers inflammation and oxidative stress that lead progressively to valve calcification.[3] Hypercholesterolemia and high plasma levels of LDL particles are associated with an increase in oxidized LDL deposition in aortic valve leaflets, causing leaflet thickening, macrophage intrusion, and calcification.[4] Another plausible mechanism is mediated by the renin–angiotensin–aldosterone system through the promotion of monocytes infiltration, inflammatory cytokines production, and differentiation of aortic valve interstitial cells into osteoblast-like cells.[5] Over time, all these processes lead to valve degeneration and calcification. Valve leaflet thickening, along with the resultant reduction in the aortic valve area, increase left ventricular afterload, which in turn leads to ventricular remodeling, fibrosis, and diastolic dysfunction. As valvular degeneration progresses in severity, systolic dysfunction ensues, and the risk of lethal arrhythmias rises. Therefore, different mechanisms are involved in the pathogenesis and progression of AS, and thus may be targeted by medical therapy. Ongoing clinical trials are currently testing the effects of medications that target calcium metabolic pathways on the progression of calcific aortic stenosis.

Medical Management of Aortic Stenosis

Previous studies have revealed an association between traditional cardiovascular risk factors, such as dyslipidemia, hypertension, and diabetes, and the development of severe AS.[6] Therefore, optimal control of these risk factors may mitigate the likelihood or delay the onset of AS. Nonetheless, no medical treatment has been proven to prevent or treat AS efficaciously.[7] For example, clinical trials evaluating the impact of statin therapy on valve-related outcomes in asymptomatic patients with mild-to-moderate AS showed no benefits, despite a significant reduction in the rates of ischemic events.[8,9]

Clinical guidelines provide no recommendations for the pharmacological treatment of AS beyond symptomatic relief and control of concomitant hypertension.[10,11] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers constitute a safe option for blood pressure control, and have been shown to have beneficial myocardial effects.[12]

When to Intervene?

Class 1 indications for aortic valve replacement are:[10,11]

- Severe AS with symptoms of exertional dyspnea, angina, or heart failure.
- Severe AS, asymptomatic, but with left ventricular ejection fraction <50%.
- Severe AS, asymptomatic, but undergoing cardiac surgery for other indications.

Class 2a indications for aortic valve replacement are:[10,11]

- Severe AS, asymptomatic, and at least one of the following: decreased exercise tolerance or ≥10 mmHg drop in blood pressure during exercise, a serum brain natriuretic peptide that is at least threefold the upper reference limit, or an increase of ≥0.3 m/s per year in blood flow velocity across the aortic valve.
- Severe AS with a transvalvular velocity of ≥5 m/s.

Class 2b indications for aortic valve replacement are:[10]

- Severe AS and a progressive decrease in left ventricular ejection fraction to <60% on three or more serial imaging studies.
- Moderate AS, asymptomatic, but undergoing cardiac surgery for other indications.

In general, symptomatic patients who undergo aortic valve replacement have a better prognosis, enhanced quality of life, and improved left ventricular systolic function.[13]

Timing and Mode of Intervention

The ideal timing of aortic valve replacement should be determined while considering several factors. First, delaying intervention in asymptomatic patients with severe AS carries a risk of adverse cardiac events (i.e. sudden cardiac death) and contributes to progressive left ventricular remodeling. Conversely, both surgical and transcatheter interventions have their own risks and complications, despite significant advances in the safety and efficacy of these therapies. In addition, all bioprosthetic valves are subject to deterioration over time, and carry a risk of endocarditis and thromboembolic events. Anticoagulation, especially with mechanical valves, is often required and is associated with bleeding-related complications. Therefore, the ideal timing of the procedure is best described as the point in the disease course when the benefits of valve replacement outweigh the risks of the procedure and the untreated native disease.

The choice between SAVR and TAVR must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient, who can then make an informed treatment choice. According to the 2020 American College of Cardiology Guidelines for the management of valvular heart diseases, SAVR is recommended for patients who are aged <65 years or have a life expectancy >20 years.[10] In patients aged between 65 and 80 years without any anatomical contraindication for TAVR, both SAVR and TAVR are equivalent, and the choice should be made based on Heart Team discussion (i.e. to balance expected patient longevity and valve durability) and the patient's preferences.[10] Finally, in those who are aged >80 years or younger patients, but with a short life expectancy (i.e. <10 years), transfemoral TAVR is recommended over SAVR.[10] To note, the 2021 European Society of Cardiology Guidelines for the management of valvular heart diseases consider age 75 years as a cut-off point, and surgical risk (low versus high) in guiding the choice between TAVR and SAVR.

Extension of TAVR Indications to Low-risk Patients

Early clinical trials have established TAVR as the best option for treating patients with symptomatic severe AS who are deemed to be at moderate-to-high operative risk, and who cannot otherwise undergo surgical replacement. In contrast, the use of TAVR in patients at low operative risk remained limited due to the lack of robust evidence.

In 2019, two randomized clinical trials comparing TAVR versus SAVR in low-risk AS patients were published: the PARTNER 3 trial and the Evolut Low-Risk trial.[14,15] The PARTNER 3 trial revealed the superiority of TAVR over SAVR at 1 year for the primary composite outcome of mortality, stroke, and rehospitalization.[15] Similarly, the Evolut Low-Risk trial showed non-inferiority of TAVR versus SAVR in the primary composite endpoint of mortality or disabling stroke at a 2-year follow-up.[14] As compared with SAVR, TAVR was associated with a higher incidence of perivalvular leak, new-onset left bundle-branch block, and need for implantation, especially with the Evolut bioprosthetic valve (Medtronic).

The clinical implications of these findings will be elucidated in the follow-up data that will be published over the next few years. In addition, patients with complex anatomy (i.e. bicuspid aortic valve, annular calcification, etc.) were excluded from these two studies, rendering the findings not generalizable to all low-risk patients with AS. In summary, the results from these two ground-breaking trials inform us that TAVR is superior to SAVR in the short term among low-risk patients with AS. The 5- and 10-year follow-up data will generate more insights on the efficacy of TAVR in these patients, and whether this less invasive approach is a true winner when compared with SAVR.

Conclusion

AS remains the leading etiology of valvular heart diseases requiring intervention in addition to medical therapy in developed countries. Over the past 20 years, multiple innovations have improved the safety and efficacy of invasive treatments for AS, with TAVR being the most notable invention. These revolutionary changes have led to recommendations for earlier intervention and expanded use of TAVR in patients with AS across the entire spectrum of surgical risk. Yet, the durability of transcatheter prosthetic valves and long-term outcomes following the procedure remain unknown. Within this context, well-conducted clinical trials with long-term follow-up are needed to better understand the optimal management of patients with AS in terms of optimal medical therapy, timing, and mode of intervention. Furthermore, current and future studies should explore the use of TAVR in patients with asymptomatic severe AS, patients with severe stenotic bicuspid aortic valve, and patients with moderate AS along with heart failure with reduced ejection fraction. ❑

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