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EDITORIAL COMMENT

Valve in Valve for Failed Surgical Bioprostheses

Not for Everyone!*

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Despite the advancements of transcatheter therapy, surgical aortic valve replacement (SAVR) remains the preferred therapy for the majority of low-risk patients with symptomatic aortic stenosis. In these patients, a choice must be made: mechanical or tissue AVR. Historically, mechanical AVR has been chosen for younger patients due to its presumed durability advantage. However, it comes at the price of increased bleeding complications associated with the need for long-term anticoagulation. Over the last several decades, there has been a shift toward increased use of bioprosthetic tissue valves, even for younger patients. From the STS (Society of Thoracic Surgeons) database, bioprosthetic valve usage increased from 43.6% in 1997 to 78.4% in 2006 (1). Over the last decade, there has continued to be increased usage of bioprosthetic valves, even among younger patients (2,3).

This shift toward bioprosthetic valves, especially in younger patients, is being fueled partially by the development of transcatheter aortic valve replacement (TAVR) technology. Valve in valve (VIV) has emerged as an alternative to reoperation in high-risk patients, and although there has been no randomized trial comparing VIV transcatheter heart valves (THVs) against reoperative SAVR, the U.S. Food and Drug Administration has approved both the Medtronic CoreValve Evolut R (Medtronic, Minneapolis, Minnesota) and the Edwards Lifesciences Sapien 3 (Edward Lifesciences, Irvine, California) THVs for this therapy in high-risk surgical candidates. However, there are some significant concerns and limitations with VIV. Although the bioprosthetic valve can serve as an ideal landing zone for the THV, the frame, in contrast to a native aortic annulus, is nonelastic and prevents complete expansion of the THV. This is especially relevant in smaller surgical bioprostheses. Initial data from the VIVID (Valve-In-Valve International Data) registry have demonstrated that residual gradients of >20 mm Hg after VIV are common (especially in surgical bioprostheses <23 mm) and are associated with increased mortality (4). It is not surprising that patients with higher gradients and smaller effective orifice areas (EOAs) have a worse prognosis, because they likely have severe patient-prosthesis mismatch (PPM). In the surgical published reports, PPM has been known to be a predictor of increased mortality and rehospitalizations (5).

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In this issue of *JACC: Cardiovascular Interventions*, Pibarot et al. (6) report data from the VIVID registry on the impact of pre-existing PPM of the surgical bioprosthesis on outcomes following valve-in-valve replacement. In this registry of 1,168 patients, 89 (7.6%) had pre-existent severe PPM as calculated using predicted EOAs for the surgical valve type and body surface area. Patients with pre-existing severe PPM were more likely to have a surgical prosthesis 21 mm or less compared with those who did not have severe PPM (77.5% vs. 26.6%). In addition, patients with severe PPM received a smaller THV on average and were more frequently treated with a self-expanding valve (CoreValve/Evolut R) over

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a balloon-expandable valve (Sapien/SXT/S3) (70.8% vs. 28.1%). The severe PPM group had a higher percentage of patients with a residual mean gradient ≥20 mm Hg (47.6% vs. 29.5%), and higher gradients were more common in those receiving a balloon-expandable valve (78% vs 34%). Patients with pre-existing severe PPM had a 2.4-fold higher mortality at 30 days as well as significantly higher 1-year adjusted mortality compared with those without severe PPM (19.3% vs. 10.9%). In multivariable analysis, pre-existing PPM was an independent predictor of 1-year mortality (hazard ratio: 1.88; 95% confidence interval: 1.07 to 3.28).

This is the first study to report an independent association between pre-existing PPM and increased mortality after VIV. A recent publication from the CoreValve US Expanded Use Study demonstrated higher gradients in patients with pre-existing PPM but did not show an association with increased mortality (7). Why the differing results? One reason may be the definition of PPM was different in the current study with higher thresholds for obese patients resulting in lower rates of pre-existing PPM (7.6% vs 13%). By being more stringent with the definition, the current study may have selected a higher-risk population. Second, the current study is much larger and thus may have had more power to demonstrate a significant difference. Finally, and perhaps most importantly, the current study, unlike the CoreValve Expanded Use Study, used both self-expanding and balloon-expandable THVs. Due to its supra-annular design, the CoreValve THV has better hemodynamics, especially in small annuli. Unfortunately, the present study did not report outcomes by valve type.

One interesting observation from this study is the time to treatment was significantly shorter (~2 years less) in patients with pre-existing PPM. This raises an important question: what was the reason these patients underwent VIV? Was it due to structural valve failure or simply due to elevated gradients? Patients with PPM of the surgical valve are likely prone to earlier failure because the elevated gradients can increase stress on the leaflets and lead to earlier degeneration. However, it is also feasible that some patients came to treatment for elevated gradients unrelated to structural valve degeneration. In these patients, the benefit of VIV will be limited because TAVR cannot correct PPM since most surgical valve frames are not expandable. In fact, the gradients may worsen as VIV may further reduce the EOA.

The current study by Pibarot et al. (6) raises the question of why pre-existing PPM should have a greater impact on outcomes than high residual gradients alone. One potential reason is that the left ventricle in patients with pre-existing PPM has been subjected to higher loads for many years and thus has remodeled negatively. Therefore, even after VIV therapy, severe PPM still exists, and the load on the LV is not relieved. This study clearly demonstrates that patients with pre-existing PPM have a worse prognosis. However, do patients that develop PPM as a result of VIV have a similarly poor prognosis? The PARTNER 2 (The PARTNER II Trial: Placement of Aortic Transcatheter Valves) VIV registry with the balloon-expandable Sapien XT valve did show higher mortality in patients with residual gradient ≥20 mm Hg but did not demonstrate a higher mortality in patients with severe PPM (8). This appears counterintuitive, but this study was confounded by the high rate of severe PPM (58.4%) following VIV, which may have diluted some of the effect. More data are needed to understand these effects.

The current study emphasizes the importance of minimizing PPM after SAVR, especially for patients who are expected to outlive their surgical valve and require further therapy. Therefore, it is important for surgeons to take measures to reduce PPM, such as choosing surgical valves with better hemodynamics or performing root enlargements in cases where PPM is expected. It is encouraging that recent data from the STS database demonstrate the rates of severe PPM after SAVR have decreased from 13.8% in 2004 to 6.2% in 2014 (9). However, it is important to note that there is still significant usage of small surgical valves. From the STS database, among patients undergoing surgical AVR between 2007 and 2010, 38.5% of patients received prosthesis <23 mm in size (2). Not only are these valves at higher risk of developing PPM, but they are also poorer candidates for VIV therapy due to their smaller internal diameter. In the current era, surgeons using a surgical bioprosthesis must ensure that the surgical result is TAVR-ready to allow for successful VIV therapy in the future. This means ensuring PPM is minimized, and larger surgical prostheses (23 mm or larger) are utilized except in rare circumstances. If it is not possible to use a larger prosthesis, then consideration should be given to doing TAVR upfront. This strategy has been shown to have lower rates of PPM when compared with SAVR (10). Alternatively, newer generation surgical valves with an expandable frame to facilitate valve-in-valve TAVR, such as Inspiris (Edwards Lifesciences) and Perceval (LivaNova, London, United Kingdom), should be considered. In order for this to happen, surgeons and cardiologists must review imaging

upfront and together to determine what is the best option for the patient, not only for the present, but also for the future.

Although efforts should be made to avoid surgical PPM, this will not be feasible in all cases. The question remains what to do when patients with severe PPM present with bioprosthetic valve failure. Consideration can be given to fracturing the surgical valve frame during TAVR to facilitate THV expansion and reduce residual gradients. Recently, publications have demonstrated that bioprosthetic valve frame fracturing is possible with high-pressure balloon inflations either before or after TAVR (11). By fracturing the valve frame, THV expansion is facilitated, resulting in lower residual gradients. However, the safety and feasibility of this procedure is not well established, and also, the impact of high-pressure balloon inflation on long-term durability of THV leaflets is unknown.

VIV for failing surgical bioprostheses is an excellent option for many patients. However, studies such as the current one demonstrate the limitations of the therapy in patients with pre-existing PPM. Reoperation could be a better solution for these patients until the safety and efficacy of novel techniques such as valve fracturing becomes clear.

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