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EDITORIAL COMMENT

Transcatheter Aortic Valves for Failing Surgical Mitral Prostheses and Mitral Annular Calcification

Good From Far But Far From Good?*

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After market approval, cardiovascular devices are commonly used for off-label indications. In this issue of *JACC: Cardiovascular Interventions*, Eleid et al. (1) report on the off-label use of transcatheter aortic valves for failed surgical mitral bioprosthetic valves or annuloplasty rings and mitral annular calcification. Although dedicated transcatheter devices are currently in development for native primary or secondary mitral valve regurgitation, there is an unmet need for patients with failed surgical mitral bioprosthesis or mitral annular calcification.

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Up to one-third of patients may require redo mitral valve surgery after a median follow-up period of approximately 8 years. The short-term mortality risk following redo mitral valve surgery is dependent on patient- and operator-related factors but has been reported to range between 8% and 12% (2).

Patients with significant mitral annular calcification are typically elderly with multiple comorbidities and as such tend to experience higher rates of cardiovascular morbidity and mortality following native mitral valve surgery. Furthermore, mitral annular calcification can negatively affect the strategic approach (repair vs. replacement) and has been associated with in-hospital mortality rates between 5% and 8% (3). Given the intermediate- to high-risk nature of patients requiring redo mitral valve surgery or mitral valve surgery in the presence of mitral annular calcifications, percutaneous transcatheter intervention may provide a more attractive option because of its minimal invasiveness and potentially lower risk for bleeding, transfusions, acute kidney injury, and atrial fibrillation.

Eleid et al. (1) report on the combined experience of 6 centers regarding the feasibility of transseptal valve replacement using a balloon-expandable transcatheter aortic valve for 60 patients with failing surgical mitral valve bioprostheses, 15 patients with failing surgical mitral valve annuloplasty rings, and 12 patients with native mitral annular calcification (1). In addition to 30-day outcomes, 1-year follow-up is provided in 40% of the patients (n = 46), thus limiting conclusions about "intermediate-term" follow-up. The investigators are to be acknowledged, however, for their eloquent and candid description of the patient selection process and the complications encountered during the pioneering phase of these procedures.

From a bird's-eye perspective, the investigators encountered the following list of complications in the 87 patients treated: left ventricular perforation (3.4%), left ventricular outflow tract (LVOT) obstruction (9.0%), hemolytic anemia in the context of LVOT obstruction (1.1%), severe mitral stenosis with post-procedural mean mitral valve gradient >5 mm Hg (47.0%), acute transcatheter valve embolization (3.4%), need for a second transcatheter aortic valve for residual mitral regurgitation (6.0%), prosthetic

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valve thrombosis (2.0%), delayed mitral valve migration with consequent severe paravalvular mitral regurgitation requiring paravalvular leak closure (1.1%), major bleeding (10.0%), and need for periprocedural cardiac surgery (6.0%). Excluding periprocedural cardiac surgery, this list amounts to 73 adverse events across the 87 patients. Notwithstanding the satisfactory clinical results at 30-day and 1-year follow-up, these observations point to the existence of significant knowledge, technical, and innovative gaps in this field.

A traditional approach to better understanding these complications is to consider device-, patient-, and operator-related factors. A transseptal delivery approach was performed in 85% of patients while positioning a Safari wire (Boston Scientific, Marlborough, Massachusetts) in the left ventricle. Given the stiffness and limited steerability of the transcatheter aortic valve systems, it is likely that left ventricular perforation occurred because of excessive forces on the guidewire or nose cone while advancing the system across the numerous bends encountered around the inferior vena cava, atrial septum, and mitral valve annulus. Whether an arterial-venous loop may have avoided this complication or further complicated the procedure is a point for discussion. Furthermore, future access to flexible and steerable delivery systems may mitigate such complications.

LVOT obstruction was observed in approximately 1 in 10 patients, mostly in those with failing surgical mitral annuloplasty rings or native mitral annular calcification. In these patients, the native mitral valve anatomy is preserved, which poses a greater risk in displacing the anterior mitral valve leaflet into the outflow tract during valve deployment. Furthermore, patients with higher left ventricular ejection fractions were found to be at greater risk for outflow tract obstruction. Not uncommonly, the risk for LVOT obstruction is uniquely observed during systolic phases on computed tomography. Several interdependent factors likely contribute to outflow tract obstruction, such as mitral annular dimensions, left ventricular dimensions and function, LVOT dimensions, outflow tract-mitral annulus angle, prosthesis dimensions, and prosthesis depth of implant and orientation. No single cutoff value for any of these variables is sufficient to predict outflow tract obstruction. Understanding the complex interplay between these risk factors is best appreciated with obtaining a neo-LVOT area by simulating prosthetic valve implantation within a gated computed tomographic scan dataset. Interpretation of the results is not straightforward. Eleid et al. (1) excluded patients with predicted reductions in LVOT area of ≥50% with simulated valve implantation. Although the community has generally adopted this cutoff reduction of 50%, the origins of this cutoff are less clear. Why not 40% or 60%? Among 116 patients enrolled in the TMVR in mitral annular calcification Global Registry presented at EuroPCR 2017, LVOT obstruction was found to be an independent predictor of mortality. Several investigators are evaluating the role of preemptive alcohol septal ablation or intentional laceration of the anterior mitral valve leaflet (LAMPOON technique) before transcatheter mitral valve intervention in patients at risk for LVOT obstruction (4).

According to the Mitral Valve Academic Research Consortium, device success requires, among other criteria, a reduction of mitral regurgitation to either optimal or acceptable level without significant mitral stenosis (i.e., post-procedural effective regurgitant orifice area of ≥1.5 cm^2 with a transmitral gradient <5 mm Hg) and with no greater than mild (1+) paravalvular mitral regurgitation. In the present series, at least 47% of patients would not satisfy criteria for device success based on a post-procedural transmitral gradient >5 mm Hg. This does not take into account other criteria of device success, such as absence of procedural mortality or stroke, proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures, absence of structural or functional failure, and no specific device-related technical failure issues or complications. Elevated transmitral gradients may stem from design issues with current transcatheter aortic valves used in the mitral position, valve size selection, and relatively small landing zones in the presence of bioprostheses, with an ensuing "Russian doll effect." Similar to valve-in-valve for the aortic position, we need to better understand patient and valve size selection to reduce the incidence of severe mitral stenosis.

Acute and delayed transcatheter valve embolization and need for a second transcatheter aortic valve for residual mitral regurgitation were noted mostly in patients with bioprosthetic ring annuloplasty devices and native mitral annular calcification. In these cases, the appropriate amount of oversizing required for adequate sealing and anchoring is less well understood because of the variability in the compliance of the landing zone. In the present series, exclusion criteria for patients with mitral annular calcification included insufficient circumferential calcification (<270° of annular circumference) and presence of an annular area too large to allow 5% to 10% oversizing with a balloon-expandable transcatheter aortic valve.

In 1 patient, inadequate circumferential annular calcification (<50%) was believed to result in valve embolization that ultimately required open surgical intervention. Quantifying mitral annular calcification in clinical practice can be challenging. Do we require 270° of continuous or noncontinuous annular calcification? Is the location of calcium important (e.g., trigonal)? Does the calcium need to be of a certain thickness?

The oversizing criteria (5% to 10% by area) used in the present series of patients with mitral annular calcification was adopted from the experience with balloon-expandable valves for transcatheter aortic valve replacement. During transcatheter aortic valve replacement, much of the anchoring and sealing is occurring within the supra-annular space (i.e., calcified leaflets). The observed oversizing occurring across the leaflets is significantly greater than the oversizing occurring at the level of the annulus. A 5% to 10% oversizing at the level of the aortic annulus may be associated with a 15% to 20% oversizing at the level of the leaflets (supra-annular sizing). In contrast, measurements of the "calcified mitral annulus" already represents the narrowest portion of the device landing zone. In these cases, we appreciate the maximum achievable percent oversizing. Whether 5% to 10% oversizing is sufficient in the mitral space can be disputed, especially in the context of large dislodgment forces provided by left ventricular contractions and large mitral orifice areas. Insufficient oversizing can be a risk factor for embolization and paravalvular mitral regurgitation.

In summary, the report by Eleid et al. (1) suggests that at present, complications are common following the implantation of balloon-expandable transcatheter aortic valves for failed surgical mitral bioprosthetic valves or annuloplasty rings and mitral annular calcification. Patient selection is currently the most modifiable "risk factor" to mitigate these complications. With growing experience, best practice patterns will emerge as we eagerly await for dedicated devices.

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