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EDITORIAL COMMENT

Next Generation Valves

What Are We Looking for?*

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Transcatheter aortic valve replacement (TAVR) is an established treatment for severe symptomatic aortic stenosis patients who are not suitable or are at high risk for surgical aortic valve replacement (SAVR) (1-3). Several ongoing studies are exploring its role in lower risk patients (4). The data that secured a place for TAVR among our standard armamentarium came from the first-generation balloon-expandable valves (BEV) and self-expanding valves (SEV). Although a decade of work has proved that TAVR is a safe and effective procedure even in very sick patients, it has some shortcomings. Paravalvular aortic leak (PVL), the inability to change the position of the implanted prosthesis, the need for a permanent pacemaker, and stroke were commonly encountered challenges, among other less frequent issues such as coronary obstruction and annular rupture.

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Investigators have focused on improving some of these shortcomings by device innovations and proper patient selection (5). The study published by Lefèvre et al. (6) in this issue of *JACC: Cardiovascular Interventions* reports the initial experience with a second-generation TAVR device that was designed to reduce PVL. Investigators attained a 30-day mortality of 1% and a 1-year mortality of only 10%, with a 1-year stroke-free survival of 86% in high-risk symptomatic severe aortic stenosis patients in their initial experience with this device. Based on this study, the Direct Flow Medical (DFM) valve appears to reduce moderate and severe as well as mild PVL substantially. Reduction in mild PVL is particularly important because moderate and severe PVL are rare in the competitive space of the newer generation valves.

The DFM valve is neither a BEV nor a SEV. It is a mechanically expandable valve that can be fully repositioned and evaluated before permanent implantation. The valve has a unique design to achieve complete sealing at the annular level, minimizing PVL formation. In this study, the investigators show that the valve can be deployed successfully in a majority of patients, with good hemodynamics and safety. Like several newer valves, the moderate paravalvular leak (PVL) rate is low: at 30 days, only 1 patient had moderate PVL. Although moderate and severe PVL have been associated with increased mortality and heart failure admissions after TAVR (7), the impact of mild PVL on clinical outcomes is controversial (8). Possible explanations for inconsistencies among the studies exploring the impact of mild PVL on mortality include 1) inaccuracy in the diagnosis of mild PVL, 2) frequent type II errors due to small study populations, and 3) other comorbidities in high-risk patients potentially masking the adverse effects of mild PVL. As TAVR indications expand for lower risk patients, elimination of even mild PVL may become necessary to have excellent long-term outcomes. On the other extreme, patients with severe left ventricular (LV) dysfunction may also benefit from elimination of PVL because even mild PVL may be

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detrimental in these patients. An advantage of the DFM valve that is similar to another new generation valve (e.g., the Lotus valve) is that it is completely recaptureable and repositionable. This capability provides an opportunity to the operator to reduce the mild PVL rates even further.

In the study by Lefèvre et al. (6), the permanent pacemaker (PPM) implantation rate after DFM valve implantation is higher than with first-generation BEV and lower than SEV. It is difficult to compare the PPM rates of the new-generation transcatheter valves because of the small numbers in most studies. The impact of PPM implantation on clinical outcomes after TAVR is a subject of debate. PPM implantation was not associated with increased mortality in early TAVR studies (9). More recent studies show that LV function recovery may be impacted negatively by PPM implantation. Data on heart failure admission, sudden cardiac death, and complications from PPM implantation remain scarce (10). Beyond the clinical implications, the PPM rate is also important due to increased cost. The need for PPM implantation has been associated with self-expanding valves, the deployment depth of certain devices, the device size in relation to the annular size, patient age, and pre-existing conduction disturbances to name a few. It appears that some modifications that decrease PVL may negatively impact the PPM rate. However, the DFM valve in this small study was not associated with a significantly increase need for PPM despite a marked decrease in PVL. Similar findings have been reported from small early experience from EVOLUTE R transcatheter aortic valve.

TAVR provides slightly better hemodynamics compared with SAVR in a number of comparative studies. Although the difference in transvalvular gradient is small between TAVR and SAVR, it may amount to an important benefit, especially for patients with small annulus sizes. There is some evidence that even moderate patient-prosthesis mismatch (effective orifice area <0.85 cm^2/m^2) can lead to increased mortality with hazard ratio of 1.19 (11). Mean transvalvular gradients after DFM valve implantation appear to be numerically higher compared with those reported in other studies (**Table 1**). Comparisons between different valve types are limited by the fact that there are no studies that compare one valve with another directly. Whether the gradients are any different in a particular valve compared with others and whether particular anatomic characteristics favor one valve over the other are debatable. The relative weakness of the inter-ring structure of the DFM valve particularly in patients with severe and bulky calcifications or the presence of a ventricular ring in very small LVOT (left ventricular outflow tract) are proposed as potential mechanisms for somewhat higher trans-prosthetic gradients. Proper patient selection and adequate pre-dilation of the native stenotic valve frequently result in optimum gradients. Recently, intra-procedural post-deployment balloon dilation has been proposed by some operators as an effective technique when optimization of the transvalvular gradients is needed.

The stroke rate in this study was numerically higher compared with other valves. However, this was a small study, so the exact risk of stroke is difficult to determine. Whether repositioning or manipulation in the aortic root increases the risk of neurologic complications remains uncertain. Stroke prevention is an evolving field, and different emboli prevention devices are being tested in clinical trials for this purpose.

There are several important lessons to be learned from the experience of evaluating new transcatheter valves. Proper imaging and patient selection are of paramount importance for the short- and long-term success of TAVR with any given valve. Precise

TABLE 1 Available Data on Selected Second-Generation Valves

	30 Days						1 Year				
Valve	Patients (n)	Mortality (%)	All Strokes (%)	PVL (%) (None, Mild, Moderate, Severe)	PPM (%)	Post-Gradient Mean (mm Hg)	Mortality (%)	Stroke (%)	PVL (%) (None, Mild, Moderate, Severe)	PPM (%)	Post-Gradient Mean (mm Hg)
S3 (12)	583	2.2	1.5	64/33/2.5/0	13	11.1	14.4	4.3	68/29/2.7/0	16.9	11.3
DFM (6)	100	1.0	6.0	79/20/1.2/0	17	12.6	10.0	9.0	68/32/0/0	20.0	12.2
Evolute R (13)	60	0	0	33/64/3/0	11.7	8.1	6.7	3.4	62/34/4/0	15.2	7.5
Lotus (14)	120	4.4	5.9	83/16/1/0	28.6	11.5	10.9	9.5	89/11/0/0	32.2	12.6
Portico (15)	102	2.9	3.9	15/73/3/0	9.8	8.7	7.8	5.9	7/87/0/0	10.8	9.9

S3 and Evolute R have been recently approved in the United States. Direct Flow Medical (DFM), Portico, and Lotus valves are undergoing randomized pivotal trial in the United States for U.S. Food and Drug Association approval.

PPM = permanent pacemaker; PVL = paravalvular aortic leak.

measurement of annulus and subannular space (landing zone for the ventricular ring) is critical for the DFM valve implantation. Similarly, because the interring space is a closed tube, special attention to the coronary height and sinus width measurements is a prerequisite in order to prevent coronary occlusions. No such complications were reported in this study, which highlights the importance of proper patient selection and pre-procedural planning. As expected from the design of the valve, there was no annular rupture or trauma to LVOT or aorta in this study.

The purpose of this study was to demonstrate the safety of the device and the feasibility of implantation without PVL. The investigators demonstrated that the device is safe and effective and that favorable outcomes are maintained for 1 year and more. However, how the DFM valve compares with other approved devices remains unanswered and will need a direct comparison trial. Although the investigators presented patient characteristics of the CoreValve and PARTNER (Placement of AoRtic TraNscathetER Valves) trials for comparison, this study in no way provides comparative data. The patient population of current study is quite different from those of the initial TAVR studies. Appropriately, the U.S. Food and Drug Administration is requiring head-to-head comparison of newer valves with commercially available valves for U.S. approval. Mortality, stroke, PVL, PPM, and hemodynamics should be compared in these trials, with the potential to collect long-term durability data. Without randomized device-to-device comparative trials, it impossible to determine from single-arm registries whether differences in outcomes are the result of different patient characteristics or distinguishing properties of the devices.

In summary, the investigators should be congratulated for providing thorough results from a new generation valve that shows great promise. Future pivotal trials with a comparator arm will provide data for valve selection in different patient populations as the TAVR field matures.

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