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EDITORIAL COMMENT

Transcatheter Pulmonary Valve Implants

The Unchained Melody*

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Andersen patented his concept for transcatheter valve implantation in the early 1990s, 10 years prior to Phillip Bonhoeffer implanting the first valve in a human subject (1); it was not in the aortic valve, as intended by the inventor, but in the pulmonary position. This occurred 2 years before the first transcatheter aortic valve implantation was done by Alain Cribier (2). In 2006, it became the first transcatheter heart valve (THV) commercially available throughout the world. Since then, there have been many transcatheter aortic valve implantation devices approved in Europe, Canada, the United States, and many other countries worldwide; paradoxically, only 1 has been approved as a transcatheter pulmonary valve (TPV).

Perhaps this disparity is correlated to the prevalence of aortic valve pathology. Truly startling is the incongruity of the age spectrum that these technologies serve, and thus, their potential clinical and socioeconomic impacts. Transcatheter aortic valve replacement (TAVR) serves a disproportionately larger population consisting of primarily elderly patients with severe aortic stenosis, whereas TPV is mostly used in a significantly smaller group composed of children and young adults with complex congenital heart disease. The clinical aim for the younger population strives to ameliorate lifelong productivity/efficacy, whereas for elderly patients, the main objective focuses on bettering the short-term quality of life. The mere difference in patient volume explains the dissimilar speed of approval process and the benefit of alternative pathways such as the Humanitarian Device Exemption (3) by the U.S. Food and Drug Administration (FDA). Irrespective of the pathway, commercial approval has significant restrictions and obligations from manufacturers. A post-approval study (PAS) is required to confirm the investigational device exemption (IDE) trial results, reflecting the increased desire for more compulsive data collection and reassessment of real-world practice, even when respectable trial data is collected. This can be easily recognized by the creation of the Transcatheter Valve Therapy Registry and mandatory participation fixed to reimbursement.

Melody TPV (Medtronic, Santa Ana, California) is a valved segment of a bovine jugular vein sewn within a balloon-expandable stent. Similar to the porcine xenograft valves, the intrinsic properties of a naturally-occurring venous valve, with very thin leaflets and deep commissures, provide good leaflet coaptation at varying diameters and allow for the treatment of a wide span of valve sizes and noncircular geometries. Surgical pericardial and the more recent TAVR valves, on the other hand, are fabricated from flat sheets of pericardium, matched for thickness and elasticity to enhance coaptation and maximize durability (4). The use of intact treated xenograft valves is a less favored design as demonstrated by the pericardial constructs for the new TAVR valves; nonetheless, their performance and durability are well established. Short- and medium-term outcomes of the Melody TPV from the IDE trial suggest significant hemodynamic and clinical improvement with good durability, low reintervention rates, and an acceptable safety profile (5,6).

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In this issue of *JACC: Cardiovascular Interventions*, Armstrong et al. (7) report the results of the PAS.

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This study was conducted in 10 centers and included a total of 120 patients, with only 100 patients receiving a Melody THV. Procedural success was no different from the IDE trial, with good hemodynamic performance maintained up to 1 year and lower reintervention rates. The authors reported a procedure-related serious adverse events (SAE) rate of 13%. When calculated using the patients who received the THV, the true SAE rate is 16%, more than double that of the IDE (6%). As noted with post-approval of other technologies and as we expand to perform more challenging and complex cases, rates of complications will likely increase. This is tempered by the accumulation of experienced operators and improved skill sets of dedicated multidisciplinary heart teams. Unlike the IDE trial, concomitant procedures were allowed in PAS and were performed in 84% of the catheterizations. They predominately included conduit pre-stenting, which likely contributed to the increased rates of contained conduit tears, the most common SAE. Whether applications of advanced imaging modalities, like 3-/4-dimensional computed tomographic angiography applied in TAVR, can play a role in the right ventricular outflow tract (RVOT) and TPV implantation and provide any benefit has not yet been evaluated.

Other SAE associated with the Melody THV have been stent fracture and endocarditis. Excessive loading forces within the RVOT and the intrinsic characteristics of balloon-expandable stent metals create an ongoing risk for stent fatigue and fracture (SF). Nearly 25% of patients treated have SF by year 1 (5,8). Consistent with historical observations, this remains to be the dominant mechanism of failure/dysfunction. The pre-stenting technique of RVOT preparation with a bare-metal stent creates an artificial conduit for Melody implantation and was achieved in 76% of patients in this study. It accounted for the significant reductions in SF rates to less than one-third (7%), and the need for reintervention, justifying its importance in TPV implantation (9).

In addition, rates of late endocarditis remain low, and compared with historical reports of nearly 9.5%, contemporary data is more promising (10). As was described in a combined analysis of the original IDE, post-market surveillance study in Europe and Canada, and the PAS reported in this issue, 5% of patients overall had definite or presumed infective endocarditis, with an annualized rate of occurrence of 2.4% per patient-year and a median duration from implant of 1.3 years (11). Nonetheless, the overall mortality rate associated with the Melody TPV endocarditis is approximated at 13% (12). The risk of THV endocarditis is likely inherent in the risk of prosthetic valve implantation in a complex patient population, exemplified by surgical bioprosthetic rates in similar positions; however, this does require further exploration and development of preventative strategies as more valves are being implanted across different positions and age groups. Achieving good stent apposition and low post-procedural RVOT gradients to reduce turbulent flow and antiplatelet therapy to reduce precipitant thrombus, serving as an infectious nidus, have been postulated (13). Also, the utilization of hybrid operating rooms in many hospitals, rather than catheterization laboratories, with trained operating room staff to maintain sterile technique, may play an additional role.

Overall, we applaud the authors in their report of this transformative technology that supports the use of the Melody THV in the real-world setting—the Unchained Melody—to delay the time until repeat open heart surgery. The magnitude of the effect of the Melody TPV on the field of congenital cardiovascular interventions has been profound, with well over 3,500 patients implanted worldwide and rapidly expanding. It has, however, been softened by the limitations inherent within the technology, but more importantly, by its approved indication of size-specific conduits, representing only a small proportion of patients requiring pulmonary valve replacement. The FDA allows the off-label use of medical devices according to physician's best judgment and practice based on scientific rationale. Good results have led to off-label extension of the Melody TPV to patients with native or nonconduit RVOT where at least a portion of the circumference is composed of native tissue, bioprosthetic valve failure with valve-in-valve implantation in pulmonic and tricuspid positions, and more recently in left-sided bioprosthetic valve failure and native positions, with potential for re-expansion in children during growth (14–20).

These descriptions of off-label use of TPV re-emphasize the difficulties with the restrictions on device use, particularly in complex patient populations such as pediatric/adult congenital and high-risk, no-alternative cases. Technological development is critical for these young patients, and finding creative ways to reach certainty about both safety and efficacy needs to be a priority. Reimbursement is becoming an even more pressing issue as the use of THVs is rapidly increasing in all valve positions. Without monetary incentive, industry will continue to shy away from investing in research for

smaller groups of patient populations whose studies face stringent governmental/FDA barriers; however, there must be alternative paths to full approval, ones that attract business opportunities, which ultimately serve as catalyst for more heavily-funded research and technology.

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