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EDITORIAL COMMENT

Transcatheter Mitral Valve Replacement

Maintaining Future Focus Despite Present Uncertainty*

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Mitral regurgitation (MR) is well known to be highly prevalent, underdiagnosed, and an increasing public health challenge via its contribution to heart failure morbidity and mortality (1). Surgical mitral valve therapy, by experienced operators, is the gold standard to reduce MR burden and has excellent long-term outcomes. Despite these data, approximately 49% of patients with severe MR are not offered surgery, primarily for fear of potential comorbidities related to surgical thoracic access and potential cardiopulmonary bypass (2).

Transcatheter aortic valve replacement (TAVR) has already revolutionized the management of aortic stenosis and has now been refined into a well-established treatment for patients with as low as intermediate surgical risk (3). Similarly, there is great hope that transcatheter mitral valve replacement (TMVR) can not only reduce the morbidity associated with surgery, but also reduce the need for prolonged hospitalization and rehabilitation.

As opposed to the ovoid semilunar aortic valve, the mitral valve relies on a dynamic interplay of an anatomically complex apparatus of leaflets, chordae tendinae, papillary muscles, 3-dimensional annulus, and a contiguous left ventricular outflow tract. MR is caused by heterogeneous degenerative or functional pathology; both of which respond very differently to surgical mitral valve repair versus replacement. This complexity poses serious challenges for nascent TMVR innovation compared with early stages of TAVR development (4). Despite this, the potential of a less invasive, less morbid, streamlined transcatheter therapy for severe MR has driven scores of medical device entrepreneurs and scientists to pursue clever strategies of reducing MR while preserving apparatus. Many of these are bioprosthetic replacements, but others target varied aspects of the pathological valve apparatus, including annular reduction, artificial chordal reconstruction, and leaflet modification, to name a few (4). Even if optimal device designs are defined, several key considerations must be resolved, such as mode of delivery, durability, defining significant paravalvular leak, quantifying incidence of leaflet thrombus formation, and identifying anticoagulation strategies post-TMVR.

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In this issue of *JACC: Cardiovascular Interventions*, Regueiro et al. (5) report long-term results of 13 patients with severe symptomatic MR who underwent TMVR with the Fortis valve (Edwards Lifescience, Irvine, California) implanted via a transapical 42-Fr delivery system under a compassionate clinical program in 5 centers in Europe and Canada. Patients were evaluated by a multidisciplinary heart team and deemed to be very high or prohibitive risk for standard surgical mitral valve repair/replacement. Anatomic suitability for TMVR was performed using echocardiography and multislice computed tomography scan, and patients were followed for 24 months. The same group previously reported initial 6 month results of TMVR in a series of 3 patients, suggesting that it was feasible and resulted in satisfactory outcomes (6).

All 13 patients (mean age 71 years, 76.9% male) had severe symptomatic MR and New York Heart Association functional class ≥III heart failure. The majority (92.3%) of mitral valve disease was classified as

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functional MR with a Society of Thoracic Surgeons score of 7.2%. Technical and device success were achieved in 76.9% and 69.2% of patients, respectively. In those patients with successful TMVR, no immediate procedural mortality or left ventricular outflow tract obstruction was noted. Patients underwent echocardiographic evaluation of the valve prosthesis before hospital discharge. Two patients who had successful valve implantation died within the first month, giving an all-cause mortality rate at 30 days of 38%. Over 2 years of follow-up, 2 additional patients died due to terminal heart failure, but no evidence of valve dysfunction was seen on echocardiography. Overall mortality rates at 1 and 2 years were 46% and 54%, respectively, but 75% of patients who had survived to 30 days remained alive at 2 years.

This is the first study, to our knowledge, to evaluate long-term outcomes and valve durability following TMVR for the treatment of symptomatic severe MR in patients at high surgical risk. MR reduction after successful TMVR was maintained over time, with no late significant recurrent MR, structural prosthesis failure or episodes of late thrombosis. However, this benefit was limited to one-half of the study population, as just over one-half of the patients died within the initial 2 years. The authors speculate that the observed mortality rate may be related to morbidity due to transapical access, early operator learning curves, and the high prevalence of noncardiac comorbidities in the studied sample. Of note, those patients who survived the periprocedural period improved their functional status and had no rehospitalization due to heart failure within 2 years following the intervention. This intriguing finding needs to be confirmed in larger studies.

The lack of centralized adjudication for the echocardiographic and clinical events, and the small sample size are important limitations of the study, as mentioned by the investigators. Of note, the goals of TMVR should be measured, not only in terms of MR reduction, but also in terms of symptomatic improvement and reduction in resource utilization such as heart failure hospitalization (4). The trauma and myocardial injury associated with the apical approach may have led to further reduction in left ventricular systolic function, thereby negating expected benefits of successful TMVR. Future adoption of TMVR technology may depend on transitioning current transapical platforms to transseptal puncture approaches to eliminate this source of morbidity. Surprisingly, no structural failures of the prosthesis or episodes of late thrombosis were observed in this study, but it is known that the sponsor has terminated further testing of Fortis due to concerns of thrombosis.

So what can be interpreted from these initial long-term results? Although mortality, especially in the short term, was high, these patients represent a population that has little tolerance for invasive injury, but otherwise face a grim long-term prognosis and a lack of any other suitable therapeutic options. For those patients who did survive long-term, there did appear to be symptomatic benefit in functional class. Although such high initial mortality may make some squeamish, it must be understood that this technology is in its infancy. Innovation will streamline device delivery to reduce ventricular injury and optimize the relationship with the valvular apparatus. As technology improves, identifying risks and benefits of TMVR in specific clinical settings will be crucial to identify patient subgroups that may benefit the most (7).

It is tempting to unfairly equate TAVR and TMVR early feasibility studies. Mitral valve disease is not usually associated with high short-term mortality and rarely results in rapid progression to death. Although it does shorten life expectancy, this occurs over years as opposed to months.(8) The high short-term mortality rate of medically managed aortic stenosis likely accelerated adoption of TAVR because patients facing imminent death suddenly had a life-saving option. This situation is unlikely to repeat for TMVR because medically managed mitral valve regurgitation 1-year survival for most patients is higher (8). Furthermore, MR is more commonly associated with ventricular dysfunction. Tricuspid regurgitation and any paravalvular leak after TMVR may be more severe compared with TAVR. Further studies will need to assess long-term heart failure symptoms in addition to mortality to understand potential clinical benefit or lack thereof.

We applaud Ribeiro et al. (5) for this important and novel study in the field of TMVR. Although high short-term mortality rates were seen, this study represents initial long-term experience with TMVR technology and should not delay enrollment in further dedicated TMVR studies, especially given the increased incidence of untreated symptomatic MR. Larger and long-term follow-up studies assessing the safety and efficacy of novel devices are warranted and ultimately we should rely on randomized trial evidence to guide our clinical decision-making process. Setting the stage for future success, will depend on the lessons learned from early stage technology today.

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