Percutaneous Mitral Valve Replacement
The revolution of the future

Transcatheter mitral valve replacement (MVR) has recently emerged as an exciting new frontier in the field of cardiac structural interventions. Although transcatheter aortic valve replacement (TAVR) is a well-established treatment option for patients with symptomatic severe calcific aortic stenosis, the experience with transcatheter MVR remains at an early stage. There have been important challenges in the development of this technology, including the complexity of the mitral valve anatomy involving a saddle oval shape, the subvalvular apparatus, the interaction with the left ventricular outflow tract (LVOT) and the aortic valve, as well as the large size of transcatheter MVR devices and large catheters for implantation. At this stage of development, all of these limit the delivery approach to transapical in most cases. The wide variety of mitral pathology, from stenosis to multiple mechanisms of regurgitation, also adds to the difficulties of valve design. Furthermore, the patients being considered for transcatheter MVR are usually high risk with multiple comorbidities, including frailty, pulmonary hypertension, or severe left ventricular systolic dysfunction, each of which negatively impact the overall clinical outcome. Despite these technical, anatomic, and clinical limitations, there has been significant progress in the last couple of years. **(Blanke et al., 2017)**

Transcatheter MVR in Failed Surgical Bioprostheses or Rings:

Patients with failed surgical mitral bioprostheses or rings have been treated with the off-label use of standard aortic transcatheter heart valve devices. The pre-existing circular frame provided by a surgical bioprosthesis and some surgical rings can be used as a landing zone and provide anchoring for a balloon expandable or newer aortic transcatheter heart valve devices. Therefore, aortic transcatheter heart valve technology has been used for this purpose prior to development of dedicated transcatheter heart valve devices specifically designed for the mitral position. Transcatheter mitral valve-in-valve and valve-in-ring have been successfully performed with aortic transcatheter heart valve in hundreds of patients worldwide. Most of the outcomes data reported come from case reports, case series, and the VIVID (Valve In Valve International Database) Registry.1-5 The most frequently

used transcatheter heart valves have been the Edwards SAPIEN family of valves (Edwards Lifesciences; Irvine, CA). The delivery approach in most patients has been transapical. Although the transseptal approach has been increasingly adopted, apical access was used in 80% of cases in the VIVID registry. The composite endpoint of 30-day survival free from moderate or severe mitral regurgitation (MR) or clinically evident LVOT obstruction was observed in 88.8% of 349 valve-in-valve and 71% of 88 valve-in-ring patients retrospectively evaluated in the VIVID registry. The MITRAL (Mitral Implantation of Transcatheter Valves) trial is a prospective Food and Drug Adminstration-approved, physician-sponsored multicenter trial evaluating the safety and feasibility of transcatheter MVR with the Edwards SAPIEN 3 valve in three patient populations: native valves with severe mitral annular calcification (MAC), failed surgical rings, and failed surgical bioprosthesis. The transvenous transseptal approach is the delivery method of choice in this trial and is being successfully utilized. Enrollment is underway, and it is expected that this trial will provide important information about the safety and outcomes of transseptal transcatheter MVR **(Webb et al., 2019)**.

How Are Patients Evaluated for Transcatheter Mitral Valve Repair or Replacement ?

Patients with symptomatic severe mitral valve disease who are not candidates for standard open mitral valve surgery may be candidates for transcatheter mitral valve repair or transcatheter MVR under a clinical trial. At this early stage of transcatheter MVR development, the safety and efficacy of transcatheter MVR remains uncertain. In contrast, transcatheter mitral valve repair with MitraClip (Abbott; Abbott Park, IL) has proven to provide similar improvement of symptoms and survival compared with surgery despite higher rates of residual MR. Therefore, with limited transcatheter MVR data at the time of this review's publication, transcatheter mitral valve repair with MitraClip should be the first choice for patients who have favorable anatomy and meet clinical indication per guidelines. The underlying pathology plays a role when deciding on transcatheter repair versus replacement because repair with MitraClip is approved only for primary MR in the United States. The role of transcatheter mitral valve repair in patients with secondary MR is being evaluated in the COAPT (Cardiovascular Outcomes Assessment of the

MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial. Therefore, patients with secondary MR who have favorable anatomy for MitraClip should be considered for participation in the COAPT trial. Patients with secondary MR who have unfavorable anatomy for mitral valve repair with MitraClip could be considered for participation in a transcatheter MVR clinical trial.

Once patients have been evaluated by a structural heart team and have been considered poor surgical candidates and poor candidates for transcatheter mitral valve repair, a cardiac computed tomography scan is obtained for careful evaluation of mitral valve annulus size, presence of MAC, modeling of the valve implant, and estimation of the risk of transcatheter MVR-induced LVOT obstruction. Patients with severe calcific mitral stenosis or regurgitation with severe MAC should be considered for inclusion in the MITRAL trial or other trial when available. Patients with MR without MAC can be considered for participation in any of the clinical trials evaluating transcatheter heart valve devices designed for the mitral position.

Next Steps:

An important next step for clinicians is to consider referring patients to transcatheter MVR clinical trials. There are no dedicated mitral devices yet well-developed enough or approved for use in practice anywhere in the world. The development of transcatheter MVR will be more difficult than TAVR and will succeed only if we support clinical trials.

Structure and function of Mitral Valve Apparatus:

The main feature of the mitral valve is the mitral apparatus, which is composed of the left atrial wall, left ventricle wall, the mitral annulus, the anterior and posterior leaflets, chordae tendinae and papillary muscles. The mechanical and metabolic balance of the valve is guaranteed by the presence of interstitial cells, which are very sensitive to mechanical information (mechanotransduction) and help in valve remodeling. The valve surface is rich in endothelial cells that communicate with interstitial cells to maintain the strength and shape of the valve. The mitral annulus is a fibrous ovoid ring located around the mitral opening, it works as a sphincter; it contracts during systole and reduces the mitral valve area by completely

closing the leaflets. At the posterior leaflet insertion, the mitral annulus is thinner than other parts of the annulus, making it more vulnerable to dilatation and resulting in inadequate leaflet closure. When severe dilation occurs, the leaflets are unable to approximate each other, and mitral regurgitation is the result ***(Schubert et al., 2017)***

Leaflets: Unlike the tricuspid valve, the mitral valve has two leaflets, the anterior leaflet, and the posterior leaflet.

The anterior leaflet is located at the posterior part of the aortic root and also fixed to it. The anterior leaflet corresponds to one-third of the annular ring and two-thirds of the valvular orifice approximately. The anterior leaflet is a semicircular shape and has a free edge without indentations; it is larger and thicker compared with the posterior leaflet. It has two zones, the rough zone and clear zone that are separated by a ridge on the atrial surface. This prominent ridge is located 1 cm from the edge of the anterior leaflet. During systole, the rough zone of the anterior leaflet will be adjacent to the posterior leaflet. ***(Schubert et al., 2017; Carpentier et al., 1995)***

The posterior leaflet comprises the other two-thirds of the annular circumference and also has the name ventricular or mural leaflet. It is in the posterior part of the two commissural areas. Different from the anterior leaflet, the posterior leaflet divides into three areas zones or segments, the basal, the clear, and the rough zones, defined as P1, P2, and P3. The rough zone is distal to the ridge and broadest at the scallops. Similar to the anterior leaflet, the clear zone in the posterior leaflet is clear on transillumination and is in the middle between the basal and rough zone. The basal zone only exists in the posterior leaflet and is located at the middle scallop between the mitral annulus and clear zone ***(Dal-Bianco et al., 2013)***

From the histological point of view, one can distinguish three layers in the leaflets of the mitral valve:

- The fibrosa, which is rigid and superficial with thick collagen fibers
- The atrial, which is thinner and towards the atrial surface, with elastic fibers
- The spongiosa, a layer consisting in particular of glycosaminoglycans (GAG) and proteoglycans.

Finally, there is another very thin layer of elastic fibers on the ventricular side, in continuity with the elastic fabric of the chordae tendinae.

Chordae tendinae:

Are part of the subvalvular apparatus, the chordae tendinae are composed of fibrous strings that originate from the papillary muscles or the ventricle wall and that its insertion is into the ventricle, the anterior leaflet, posterior leaflet, and commissural leaflet. Two kinds of chordae tendinae are distinguished based on their insertion into the leaflets. The primary or marginal chordae are thinner and are attached to the leaflets at the free edge, preventing leaflet edge to prolapse for its characteristic of being high collagen fibers with reduced tension. ***(Liao et al., 2003; Lam et al., 1970)***

The secondary or intermediary chordae are thicker than primary chordae and are more extensible due to the more tightly collagen they have. The secondary chordae are attached to the ventricle aspect of the leaflets and help to reduce tension at the leaflet. ***(Millington-Sanders et al., 1998; Degandt et al., 2007)***

The chordae consist mainly of elastin and crimped collagen fibers. Chordae tendinae can have six classifications: depending on the origin they can be apical and basal; depending on the area concerned, true or false; depending on the anatomical attack they are cusp, cleft and commissural; depending on the interest of the valve area they are first-order chordae or second-order chordae; depending on the shape they can be straight, branched, dichotomous or irregular; and depending on the constitution they can be tendinous, muscular, or membranous.

Blood Supply and Lymphatics

Two papillary muscles are part of the mitral valve, the anterior and posterior papillary muscles, and each of them provides tendon cords for both valve leaflets. The anterior papillary muscle receives vascular supply via the anterior descending artery and the circumflex artery, which is a branch of the left coronary artery, while branches of the right coronary artery vascularize the posterior papillary muscle. Dysfunction of blood supply can damage the valve. ***(Rusted et al., 1952)***

Nerves

The autonomic nervous system modulates the mechanical properties of the mitral valve, thanks to the release of neurotransmitters from nerve ends. The stiffness of the valve decreases in the presence of acetylcholine, while it increases in the presence of norepinephrine***.(Gorman et al., 1996)*** Aging reduces valve innervation.

Muscles

The main muscular structures that are part of the mitral apparatus are the papillary muscles and the left ventricular wall. The papillary muscles derive their names from their relationship with the mitral commissures. They originate from the apical portion of the left ventricle, and there are two, the anterolateral papillary muscle and the posteromedial papillary muscle. ***(Rusted et al., 1952; Victor et al., 1995)***

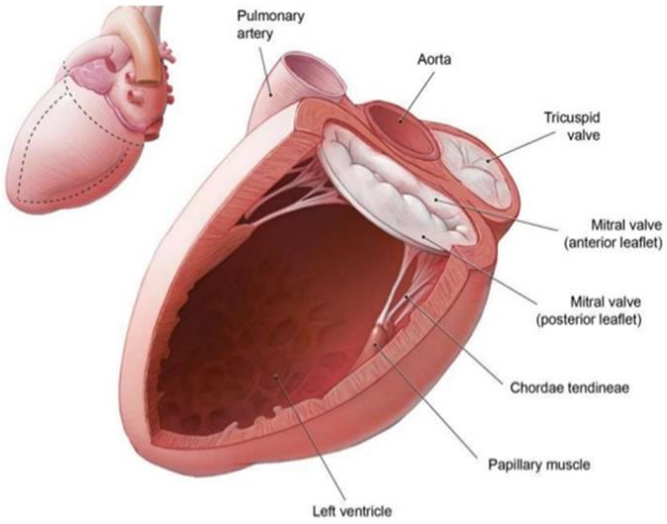
The papillary muscles system coordinates with the mitral annulus, so in every contraction during systole, this system prevents leaflet prolapse. As part of the mitral apparatus, the papillary muscles and all the other components of mitral apparatus work in a way to maintain valvular competence and the proper blood flow. On the other hand, if a fusion of the papillary muscles exists, it will result in stenosis of the mitral valve, and if there is a rupture of the papillary muscles, common as a complication of myocardial infarction, will result in mitral regurgitation.***(Komeda et al., 1997)***

Surgical Considerations

Mitral Regurgitation is associated with an abnormal backflow of blood from the left ventricle to the left atrium. In developed countries, the main cause is ischemic coronary disease, and in undeveloped countries, the main cause is a rheumatic disease. Mitral regurgitation in the United States is present in approximately 2 million people and is the second most common valvular disease, after aortic stenosis. ***(Enriquez-Sarano et al., 2009)***

In functional mitral regurgitation the mitral valve leaflets and the mitral annulus apparatus are normal, but there is an abnormality of the ventricular wall, that results in a dysfunction between the wall motion, the papillary muscles and the annulus that increases the distance of the annulus and papillary muscles that results in the restriction of the leaflet motion. On the other hand, rheumatic mitral regurgitation is an acquired disease that presents with stenosis of the mitral valve, in this case, the leaflets are thickened and rigid, the chordae tendinae become shortened due to fibrosis as a result of inflammatory changes. There is also calcification of the leaflets and the mitral valve apparatus that can result in leaflet dysfunction and causes leaflet motion restriction and regurgitation. ***(Sabbah et al., 1992)***

Symptoms of mitral regurgitation depend on the left ventricle function; patients can present with dyspnea, fatigue, and orthopnea. Patients with severe disease can progress to congestive heart failure with pulmonary congestion and edema. On auscultation of a patient with mitral regurgitation, the S1 may appear diminished, and a classic finding is a holosystolic, high-pitched murmur due to early closure of the aortic valve. ***(Sabbah et al., 1993)***



(Figure 1) Structure of Mitral Valve Apparatus

The Need for Trans catheter Mitral Valve Replacement

Transcatheter mitral valve replacement (TMVR) for native mitral regurgitation (MR) is a transformative technology with early feasibility now established for multiple platforms and devices. Recent reports have described near complete abolishment of MR with TMVR therapy, leading to mild or no symptoms in ~75% of survivors in early clinical follow-up ***(Cheung et al., 2014; Abdul-Jawad AO et al., 2015; Muller DWM et al., 2017; Bapat V et al., 2018)***

The enthusiasm for TMVR, among other transcatheter approaches, is considerable due to the high prevalence of MR patients, their poor prognosis without therapy, and belief that MR correction improves not only symptoms of heart failure, but also survival ***(Nkomo et al., 2006; Enriquez-Sarano et al., 2005; Goel et al., 2014; Mirabel et al., 2007; Stone et al., 2018)*** Importantly, the societal burden of patients with MR, which is an age-dependent disease, is only expected to grow with changing population demographics. Thus, there is hope that further TMVR development for native MR will help to address current and growing unmet clinical needs for these patients.

To date, the overwhelming majority of TMVR cases have been performed using a transapical approach, which facilitates both placement of large-bore delivery sheaths as well as coaxial alignment of the prosthesis relative to the native mitral annulus. The transapical approach for TMVR poses some technical challenges. Unlike aortic stenosis, the pathophysiology of MR is volume hypertrophy, with left ventricular myocardium that is typically not thickened.

For coaxial alignment, the left ventricular access point for TMVR is usually remote from the true apex and often on the free wall ***(Blanke et al., 2017)*** With the size of current delivery sheaths (i.e., commonly >32 F), relatively stretched thin myocardium, and this access point location, bleeding is a concern for transapical (or "transventricular") TMVR, and has been associated with operative mortality in early experience. Moreover, although TMVR is a transcatheter method that does not require cardiopulmonary bypass, the post-operative recovery (i.e., >1 to 4 days in the intensive care unit) and early mortality (i.e., 6% to 14%) with the transapical approach more closely mimics that of open surgery rather than that of other percutaneous valve therapies ***(Cheung et al., 2014; Abdul-Jawad AO et al., 2015; Muller DWM et al.,***

2017; Bapat V et al., 2018).

The transition of TMVR into a transvenous, trans- septal approach is an expected evolution for the therapy. Potential attractive features for transseptal TMVR are less bleeding from avoidance of large bore injury to the left ventricle or femoral artery and an expedited post-procedural recovery. Importantly, the transseptal approach also carries the potential for therapeutic expansion by minimization of the various surgical resources needed to complete the procedure. To be sure, transseptal approaches for TMVR in the treatment of native MR have been in development for years, with clinical success already demonstrated for several technologies (e.g., Caisson, LivaNova London, United Kingdom; CardiAQ, Edwards Lifesciences, Irvine, California). These technologies have been able to overcome steering and imaging challenges, with a considerable amount of leverage gained from operator experience with other transcatheter mitral therapies, such as MitraClip (Abbott Structural, Santa Clara, California), valve-in-ring therapy, and valve- in-valve treatment for degenerated surgical mitral prostheses. Indeed, U.S. approval for commercial mitral valve-in-valve therapy first occurred in 2014, and it is estimated that over 3,000 patients have already undergone such therapy thus far

In this issue of the *Journal,* Webb et al. ***(Webb et al., 2019)*** describe successful use of a novel transseptal TMVR therapy, the Sapien M3 (Edwards Lifesciences, Irvine, California). The M3 device is similar to the Sapien S3 prosthesis already in use, but it has the advantages of a nitinol dock for anchoring in the native mitral apparatus, and an external, knitted cloth to promote sealing and prevention of paraprosthetic regurgitation. The nitinol dock is a key feature that allows circularization of the irregular mitral valve orifice, and it does so without distension of the mitral annulus. Other TMVR platforms commonly rely on mitral annular *oversizing* for anchoring and for reducing paraprosthetic regurgitation; such oversizing is wholly different from traditional open surgery, in which downsizing typically is performed. It has been theorized that there might be a beneficial effect on ventricular loading conditions when there is less or no mitral annular distension, though this possibility is completely unexamined. At the very least, less mitral annular oversizing is associated with lower device profile and, thus, less potential for left ventricular outflow tract obstruction, which is a common exclusion for TMVR candidacy ***(Blanke et al., 2017)***

The report by Webb et al. ***(Webb et al., 2019)*** demonstrates the feasibility of the M3 system, with promising clinical success for a transseptal TMVR approach and early post-operative discharge. Certainly, the study was small (n = 10) and only from a single center. Only 1 prosthesis size (i.e., 29 mm) was tested, with no information on the treatable range of patients. Presumably, there is mitral valvular and subvalvular anatomy not suitable for the nitinol dock, and some native leaflets may not seal well around the prosthesis. Also, although nearly all patients had procedural success, 1 patient had severe mitral stenosis, and the average gradient for all implants was 5.8 mm Hg, which is higher than observed in other TMVR studies ***(Muller DWM et al., 2017; Bapat V et al., 2018)***

The details on anatomical selection and screen failure rates will need to be examined in larger patient populations. Prior transcatheter experience with Sapien prostheses in native mitral valves has predominantly occurred in high-risk patients with severe mitral annular calcification, a very difficult anatomical subset, and in whom the embolization or malposition occurs in 20%, the rate of LVOT obstruction is 9%, and there is a 30-day mortality of 30% ***(Guerrero et al., 2016)***. Given the novel technical advancements, one hopes that the clinical experience with the M3 system will more closely resemble that of mitral valve-in-valve therapy, in which technical success is >95% ***(Paradis et al., 2015)***. The latter findings would be welcomed, especially as the M3 importantly leverages operator experience with a transcatheter delivery system that is already in widespread use.

The arrival of technology like the M3 system gives us a glimpse of what will be possible for the treatment of MR in the very near future. A technical solution for transvenous, transseptal TMVR is a certainty. What is unknown, however, is the degree to which TMVR will complement or even supplant transcatheter repair approaches in high-risk patients, and its likelihood as an alternative for surgical-eligible patients in whom a replacement strategy is preferred. Aside from technical success, there will be a need for rigorous, scientific study to determine the incremental clinical benefit that may occur with complete relief of MR, which is greater with replacement strategies than with current transcatheter repair techniques ***(Sorajja et al., 2016; Nickenig et al., 2011)*** That benefit will have to be weighed against any concern regarding leaflet durability and potential prosthetic complications, such as leaflet thrombosis, bleeding, and endocarditis. The weight of these concerns will differ

according to mitral anatomy, life expectancy, surgical risk, health economics, and quality of life, whether the patient is treated in a referent center or not, as well as the technical ease and safety of the procedure. Consideration of the life-saving results recently demonstrated with transcatheter mitral valve repair in selected patients will be essential ***(Stone et al., 2018; Obadia et al., 2018).*** Finally, an important factor also will be how much the transcatheter repair strategy permits future transcatheter replacement, which could be needed to address residual or recurrent MR after unsuccessful repair.

Presently, for patients with MR who have surgery, many have mitral valve replacement, and a tissue prosthesis is used in >90% of cases. Nonetheless, despite available surgical therapy, we have millions of untreated patients with MR and whose prognosis is poor without treatment. Thus, there is no doubt that there will be a role for TMVR like the M3 system in the management of patients with MR. Like other transcatheter valve therapies, TMVR has clinical promise that may help to address unmet clinical needs for patients with MR. Given demonstrated feasibility, the forthcoming scientific inquiry on TMVR will be about determining which needs those are exactly.

Transcatheter Mitral Valve Replacement

Maintaining Future Focus despite Present Uncertainty

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 ***(Nkomo et al., 2006).*** 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 ***(Mirabel et al., 2017)***.

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 ***(Leon et al., 2016)***. 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 ***(Herrmann et al., 2017)***. Despite this, the potential of a less invasive, less morbid, streamlined trans catheter 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 ***(Herrmann et al., 2017)***. 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.

In this issue of *JACC: Cardiovascular Interventions*, Regueiro et al. ***(Regueiro et al., 2017)*** 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 ***(Abdul-Jawad Altisent et al., 2015)***.

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 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 echocar- diographic 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 echo- cardiographic 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 ***(Herrmann et al., 2017)***. 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 longterm 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 ***(Maisano et al., 2015)***.

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.***(Anyanwu et al., 2018)*** The high short-term mortality rate of medically managed aortic stenosis likely accelerated adoption of TAVR because patients facing imminent death suddenly had a lifesaving option. This situation is unlikely to repeat for TMVR because medically managed mitral

valve regurgitation 1-year survival for most patients is higher ***(Anyanwu et al., 2018)***. 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. ***(Regueiro et al., 2017)*** for this important and novel study in the field of TMVR. Although high shortterm 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 longterm 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.

Percutaneous Transcatheter Mitral Valve Replacement

First-in-Human Experience With a New Transseptal System

Symptomatic mitral regurgitation (MR) conveys significant morbidity and mortality ***(Agricola et al., 2009).***However, many patients with severe MR are not treated with surgery due to advanced age, left ventricular (LV) dysfunction, or other comorbidities ***(Mirabel et al., 2007)*** This unmet clinical need has driven the development of safer, catheter-based treatments for mitral valve disease.

Transcatheter mitral valve repair can be safe and effective in patients with suitable anatomy ***(Feldman et al., 2011)*** However, many patients have unsuitable anatomy and repair may be difficult, unsuccessful, or temporary. ***(Stewart et al., 2016; Beigel et al., 2014)*** Transcatheter repair is associated with lesser degrees of MR reduction, which may be associated with poorer clinical outcomes and durability ***(Grasso et al., 2006)*** . Although surgical mitral valve repair is often preferred over surgical replacement ***(Nishimura et al., 2017),*** the relative benefits and risks in patients undergoing transcatheter replacement and repair are unknown.

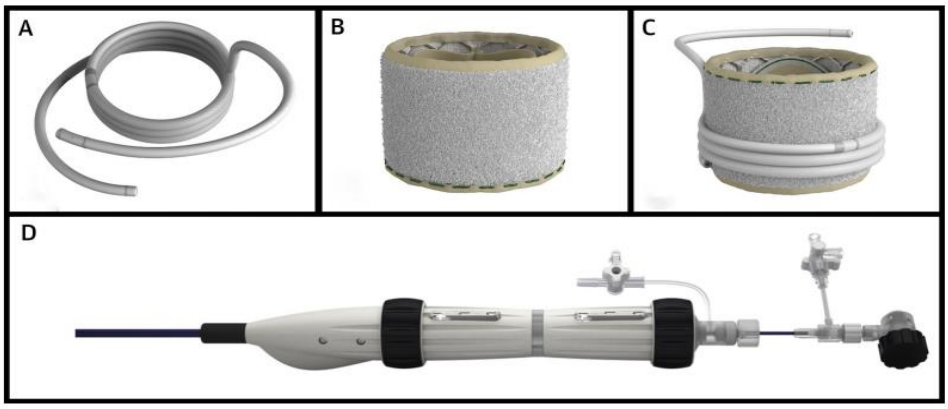
Early experience with transcatheter mitral valve replacement (TMVR) has suffered, in part, due to the limitations of apical access and the associated thoracotomy. For patients with prior surgical valve replacement or repair valve-in-valve or valve-in-ring procedures are proven options, and for those with severe mitral annular calcification, valve-in mitral annular calcification is sometimes feasible. ***(Yoon et al., 2019; Cheung et al., 2016)***

Building upon substantial experience with mitral valve-in-valve and valve-in-ring procedures utilizing the balloon-expandable Sapien 3 transcatheter heart valve (THV), we report the first-in-human experience with a percutaneous transseptal TMVR procedure (Edwards Sapien M3, Edwards Lifesciences, Irvine, California).

This first-in-human study was conducted at the Centre for Heart Valve Innovation, St. Paul's Hospital, Vancouver, Canada, between August 2017 and August 2018. Patients included were age >18 years, with severe MR and symptoms of heart failure (New York Heart Association functional class 2). All patients were reviewed by a multidisciplinary heart team and considered: 1) suitable for mitral valve intervention; 2) at high or prohibitive surgical risk; and 3) not ideally suited to other

available transcatheter mitral valve interventions (i.e., edge-to-edge repair, trans-apical TMVR). Exclusion criteria were LV end- diastolic diameter >70 mm and LV ejection fraction <30%. Anatomical feasibility was determined using transesophageal echocardiography (TEE) and computed tomography (CT) imaging: patients with severe mitral leaflet calcification, unsuitable chordal anatomy, high risk of left ventricular outflow tract (LVOT) obstruction, or unfavorable mitral valve anatomy were also excluded.

Figure (2): The Transseptal Transcatheter Mitral Valve, Dock, and Delivery Catheter



The transseptal transcatheter heart valve consists ofa nitinol dock **(A)** and PET-covered balloon expandable transcatheter heartvalve **(B)**, which form an ensemble **(C)**, anchoring and sealing by incorporating the native mitral valve leaflets. The delivery system **(D)** allows 3-dimensional control of the catheter tip and controlled exposure of the dock, with complete recapture if necessary.

Table (1): Baseline Characteristics

Age, yrs	76.1 ± 5.5
Sex	
Male	5(50)
Female	5(50)
Hypertension	6 (60)
Coronary artery disease	
Myocardial infarction	4 (40)
Percutaneous coronary intervention	3(30)
Coronary artery bypass grafting	3(30)
Atrial fibrillation	3(30)
Pulmonary hypertension	4 (40)
Cerebrovascular disease	1 (10)
Chronic pulmonary disease	4 (40)
Chronic kidney disease	4 (40)
Body mass index, kg/m^2	27.0 ± 3.2 (n = 10)
STS predicted risk of mortality, %	3.8 ± 2.5 (n = 10)
EuroSCORE II, %	5.9 ± 2.2 (n = 10)
NYHA functional class	3(3, 3) (n = 10)
6-min walk distance, m	288 (252, 370) (n = 9)
Kansas City Cardiomyopathy Questionnaire-12	51.00 (42.45, 62.85) (n = 8)
Values are mean ± SD, n (%), or median (Q1, Q3). NYHA = New York Heart Association.	

The device:

Utilizing percutaneous femoral venous access, a transseptal deflectable sheath is placed in the left atrium. A steerable catheter is then advanced just under the posteromedial mitral commissure (Figure 1). Using fluoroscopy and TEE guidance, the expandable polytetrafluoroethylene-covered nitinol “dock” is advanced under the anterior mitral leaflet. As the nitinol dock is advanced into the left ventricle, it assumes its pre-determined shape and encircles the chordae tendineae below the level of the mitral annulus. The dock is a single component with 3 distinct sections: a leading turn has a larger diameter (37 mm) to capture the chords, subsequent functional turns have a smaller diameter (25.5 mm outer diameter) and provide the anchor for the balloon- expandable THV. A polyethylene terephthalate braid covering the functional turns of the dock increases retention forces and prevents migration. A final atrial turn helps maintains dock position prior to THV deployment. While connected to the delivery catheter, the dock is fully retrievable.

After release of the dock, a balloon-expandable bovine pericardial leaflet THV is advanced through the transseptal sheath and deployed during rapid ventricular pacing. The transseptal TMVR system ensemble secures the native mitral valve leaflets between the dock and THV frame. Sealing occurs between the native mitral valve leaflets and a knitted (polyethylene terephthalate) cloth outside of the THV frame (Figure 2). The Sapien M3 valve is identical to the 29-mm diameter Sapien 3 aortic THV, with the addition of an external knitted PET seal which covers the entire outer surface of the valve frame. Implantation of the transseptal TMVR system is very similar to implantation of the Sapien 3 THV in failed mitral surgical bioprostheses or rings, a procedure with which there is extensive experience

Clinical follow-up was performed in-hospital and at 30 days for all patients. Transthoracic echocardiography was routinely performed pre-discharge and at 30 days, and CT between discharge and 30 days. All patients were treated with oral anticoagulation postprocedure. The primary endpoint for the study was technical success as defined by Mitral Valve Academic Research Consortium (MVARC) criteria at completion of the index procedure. The secondary endpoint was successful device implantation and freedom from mortality, stroke, and device dysfunction (MR grade >1, mitral gradient >6 mm Hg, LVOT gradient >20 mm Hg) at 30-day follow-up. Periprocedural complications were defined as per

MVARC criteria ***(Stone et al., 2015)***

Research was conducted in compliance with the Declaration of Helsinki for human investigation. Patients provided written informed consent. Research approval was granted by the institutional ethics review board.

Statistical analysis:

Continuous data are presented as median (Q1, Q3) or mean ± SD; categorical variables are presented as count and percentage. Comparisons between baseline and 30-day parameters are made using the Wilcoxon signed-rank test.

- H0: the median difference = 0
- H_a: the median difference ≤ 0
- The 2-sided test was performed at alpha = 0.05. Statistical analysis was performed using R and SAS.

Results:

Baseline characteristics

Ten patients were included in the study cohort, mean age 76.1 ± 5.3 years (range 69 to 87 years). A total of 5 patients (50%) were men. Patients were judged to be at high or prohibitive surgical risk by at least 2 experienced cardiac surgeons. Mean Society of Thoracic Surgeons

(STS) predicted risk of mortality was 3.8 ± 2.4% (range 1.2% to 9.8%) and EuroSCORE II was 5.9 ± 2.1%. Baseline characteristics and comorbidities are listed in Table 1.

MR was graded severe (4 of 4) in all 10 patients. MR etiology was degenerative in 4 (40%), functional in 4 (40%), and mixed in 2 (20%). Of those with degenerative MR, the underlying pathology was prolapse, flail segment, leaflet retraction and flail segment, leaflet perforation (prior endocarditis) and flail segment, and calcification. LV systolic function was moderately impaired (LV ejection fraction 30% to 50%) in 6 (60%), and regional wall motion abnormalities were present in 4 (40%). Median (Q1, Q3) LV end-diastolic diameter was 60 mm (52 to 63.75 mm; range 45 to 65 mm). Mitral annular area by CT was 12 ± 2.3 cm^2 (range 8.5 to 15.1 cm^2).

Procedural outcomes.

The primary endpoint was achieved in 9 of 10 patients (90%) (Central Illustration). Total MR was reduced to trivial (0 of 4) in all implanted patients, and mean mitral gradient by TEE was 2.3 ± 1.4 mm Hg. Concomitant paravalvular leak closure was not required in any patients, and iatrogenic atrial septal defect (ASD) closure was performed in 3 patients (30%) for ASD $10 mm or bidirectional intera-trial flow. Total procedure time was 220 ± 45 min, fluoroscopy time was 57 ± 24 min, and total contrast volume was 72 ± 38 ml.

Table (2): Clinical Outcomes at 30 Days

Death	0 (0)
Stroke	0 (0)
Myocardial infarction	0 (0)
Bleeding (MVARC Primary Bleeding scale)	
Type I	1 (10)
Type II	0 (0)
Type III	0 (0)
Type IV	1 (10)
Type V	0 (0)
Mitral valve embolism or migration	0 (0)
Mitral valve surgery	0 (0)
Readmission to hospital	0 (0)
NYHA functional class	2(1,2) (n = 8)
6-min walk distance, m	350 (240, 402) (n = 7)
Kansas City Cardiomyopathy Questionnaire-12	73.45 (65.1, 80.78) (n = 8)

Values are n (%) or median (Q1, Q3).
MVARC = MitralValveAcademic Research Consortium; NYHA = NewYork Heart Association.

A pericardial effusion occurred in 1 patient during dock deployment: the dock was removed successfully, pericardiocentesis performed, and procedure terminated. The patient was discharged on day 2 to continue on medical management. No other procedural complications occurred. Median length of stay was 1.5 days.

30-Day outcomes.

The secondary endpoint (successful device implantation and freedom from mortality, stroke, and device dysfunction [MR grade >1, mitral gradient >6 mm Hg, LVOT gradient >20 mm Hg]) was met in 7 patients (70%). At 30 days, there was no death, myocardial infarction, stroke, rehospitalization, or LVOT obstruction.

In patients receiving the device, mitral regurgitation was mild in 8 (89%) and severe in 1. At 1 month, 1 patient had severe paravalvular regurgitation secondary to a leaflet or chordal tear (A1 scallop) adjacent to an area of calcification. A 12-mm

Amplatzer Vascular Plug II (Abbott Vascular, Minneapolis, Minnesota) was implanted with MR reduced to moderate. No other device-related complications occurred: there was no device migration, embolization, or conversion to mitral surgery (Table 2).

Median transmitral gradient at 30 days was 6 mm Hg (Q1, Q3: 5, 6 mm Hg). One patient had an elevated mitral gradient at 30 days (10 mm Hg) with normal leaflet motion, no MR, and no thrombus detected on multiphase CT. No patients had clinical or echocardiographic evidence of LVOT obstruction. Pre-procedure and post-procedure LVOT gradient by TTE doppler assessment were not different (3.5 [Q1, Q3: 3.25, 6.00) vs. 5 [Q1, Q3: 2, 6]; p = 1.00) (Table 3).

Table (3) Echocardiographic Findings at Baseline and 30 Days

	Baseline	n	30 Days	n	p Value
LVEF, %	43.5 (35, 60)	10	33 (30, 45)	9	0.125
LVEDD, mm	60 (52, 63.75)	10	60 (53, 65)	9	0.621
LVESD, mm	47.4 (33.5, 53)	10	47 (36, 58)	9	0.82
Mitral regurgitation severity, grade	4 (4, 4)	10	1 (0,1)	9	0.0078
Mitral valve gradient, mm Hg	N/A		6 (5, 6)	9	N/A
LVOT gradient, mm Hg	3.5 (3.25, 6)	10	5 (2, 6)	9	1.00
Pulmonary artery systolic pressure	50 (37, 55)	9	47 (33, 51.25)	8	0.30

Values are median (Q1, Q3) unless otherwise indicated.
LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVOT = left ventricular outflow tract.

One patient remained in the hospital after the index procedure due to oropharyngeal bleeding related to TEE and required blood transfusion (2 U; MVARC minor bleeding) and antibiotics for ventilator- acquired pneumonia.

Functional status was improved at 30 days (median New York Heart Association functional class III vs. II; p = 0.020). The 6-min walk distance and Kansas City cardiomyopathy questionnaire (KCCQ-12) were unchanged from baseline (median 288 vs. 350; p = 0.812; and 51 vs. 73.45; p = 0.195, respectively).

Post-procedural CT demonstrated a well-seated transseptal TMVR system ensemble in all cases, with no evidence of malpositioning or migration. Neo- LVOT area was 5.1 ± 2.3 cm^2, and no patients had a neo-LVOT area <1.5 cm^2.

Discussion

This study investigated the feasibility of a new transcatheter mitral valve replacement system in patients with severe MR who were at high risk with conventional surgery and unsuitable for other available transcatheter procedures

(edge-to-edge repair or transapical TMVR). The important findings of this study are: 1) transseptal TMVR is feasible with an early procedural success rate of 90%; 2) results were achieved across a variety of mitral regurgitation etiologies, both functional and degenerative (chordal, leaflet, calcification); 3) the procedure is safe, with few procedural complications in this high-risk cohort and no deaths at 30 days; and 4) early discharge is possible with median length of stay of 1.5 days.

The transseptal TMVR procedure has several potentially desirable features. First, a transfemoral transseptal approach is less invasive with less morbidity and recovery time than conventional surgery or transapical TMVR. Similar to percutaneous mitral plication, patients remain hemodynamically stable for long periods, blood loss is minimal, and the left ventricle is not compromised. Of interest, MR was often reduced after the first turn of the dock encircled the mitral chords, consistent with a variable annulo- plasty effect.

The transseptal TMVR valve represents a relatively minor modification of the 29-mm Sapien 3 aortic THV, with its well-documented reliability, hemodynamic function, and durability. As anchoring of the THV relies primarily on the 26-mm diameter dock encircling the mitral leaflets and chords, mitral annular dimensions are relatively less important, and the single 29-mm diameter transseptal TMVR system is suitable for a relatively broad range of ventricular anatomies.

As with all prosthetic mitral valves, LVOT obstruction is a concern and must be screened for. However, there are 2 major factors that mitigate against this risk: 1) the axis of the transcatheter valve is routinely biased toward the shorter posterior native mitral leaflet and away from the longer anterior leaflet; and 2) the encircling dock pulls the anterior leaflet posterior away from the LVOT. Focused echo-cardiography and routine pre- and post-implant invasive assessment did not find evidence of LVOT obstruction.

Study limitations.

This is a single-center study with a small cohort of patients. Each case was carefully reviewed to ensure clinical and technical suitability. The 30-day outcomes are reported, and longer-term clinical and valve durability outcomes will require further study.

Conclusions

Percutaneous transseptal transcatheter mitral valve replacement is feasible and may offer a relatively safe option in patients with MR who are at high risk for surgery. Early safety and efficacy are acceptable, and further study in a larger cohort of patients is warranted.

Transcatheter Mitral Valve Replacement

The Beginning

Mitral regurgitation (MR) is frequent and is undertreated, particularly in elderly patients with comorbidity or in patients experiencing left ventricular (LV) dysfunction ***(Dziadzko et al., 2018)***. This unmet clinical need led to the development of transcatheter interventions over a decade ago. Transcatheter mitral valve repair is developing much more rapidly than transcatheter mitral valve replacement (TMVR). Currently, more than 30 TMVR devices are under development, <10 of which are at a clinical stage.

The study by Sorajja et al. ***(Sorajja et al., 2019)*** in this issue of the *Journal* reports the results of the first 100 patients treated using the Tendyne TMVR system (Abbott Vascular, Santa Clara, California), which represents the largest experience with TMVR for the treatment of native MR to date. This report complements a previous publication on 30-day outcomes for the first 30 patients ***(Muller et al., 2017)*** and adds 1-year follow-up data.

Patients were at high or prohibitive surgical risk and mostly had secondary MR. Exclusion criteria included LV end-diastolic diameter >70 mm, severe mitral annular or leaflet calcification, previous mitral or aortic valve surgery, intracardiac thrombus, pulmonary artery systolic pressure >70 mm Hg, severe tricuspid valve regurgitation, severe right ventricular dysfunction, and left ventricular ejection fraction (LVEF) <30%. A total of 302 patients were enrolled and >210 patients had screening failure. The reasons for screening failure were mainly related to the risk of left ventricular outflow track obstruction (LVOT) or annular dimensions that were out of the treatable size with the currently available device. The limited information available suggests that the rate of rejection in TMVR series ranges from 60% to 70%, due to anatomic exclusions in 20% to 50% of cases and due to clinical or other causes in 20% to 40% of cases ***(Bapat et al., 2018; Urena et al., 2018)***. A strict selection is desirable to avoid early failures and complications due to anatomical features and to avoid poor midterm results of valve intervention in patients treated at a too advanced stage ***(Goliasch et al., 2018)***. Conversely, such a selection raises the problem of the applicability of the technique in real life. Information about screening failures will allow determination of which failures are due to the technique, and thus potentially

correctable with improvement in technology. In this study, as in the published data, no data exists as to whether the patients selected for TMVR were considered suboptimal candidates for transcatheter repair.

All TMVR were performed via transapical approach (TA), which is needed due to the prosthesis design and more generally due to the use of large-bore catheters (34- to 36-F). The TA approach, which is currently the default approach for TMVR, provides an easy access to the mitral valve but may induce apical complications and negatively affect the LV function. The alternative transseptal approach is less invasive, but also has limitations due to the sheath sizes and intracardiac maneuverability, which hopefully will improve in the future.

Technical success was high (96%), with all failures occurring in the first 40 patients. The procedural time was quite short. This likely results from experience and from the potential for removability and retriev- ability of the device

TMVR was able to suppress MR in all but 1 patient, in whom the prosthesis was misaligned leading to a mild MR at discharge, which increased to moderate at 3 months and was treated percutaneously.

Safety was good as shown by the absence of intraprocedural deaths, device embolization, or LVOT obstruction, and a low rate of severe apical bleeding thanks to the prosthesis design and procedural modifications.

Follow-up (FU) data (mean 13.7 months) are encouraging: at 1 year, 88% of the survivors were in New York Heart Association functional class I to II, with a significant improvement in functional capacity and quality of life. There was no echocardiographic sign of prosthetic dysfunction.

However, all-cause 1-year mortality was still high (26%), with most deaths of cardiac origin and due to heart failure in 7 of 26 patients. Finally, heart failure rehospitalizations occurred in 31% of cases. In parallel, although there was an improvement in LV dilatation, LVEF decreased. A comprehensive interpretation of these findings is difficult at this stage due to the limited number of patients and due to the absence of information on medical therapy after intervention. It is likely that the origin of heart failure is multifactorial: late progression of the LV dysfunction due to a late operation, “pop off effect,” and LV apical injury. Recurrence of MR is unlikely because there was no evidence of MR >1+ among the patients who died or who had

heart failure in follow-up.

A total of 3 patients had evidence of valve instability requiring reinterventions to increase tension on the tether. This complication was rare, but may be a concern due to the effect of LV remodeling on the tether tension with time. A thrombus was detected in 6 patients. Because echocardiography did not show an increase in valve gradient, they were probably nonobstructive. This complication did not occur again after the systematic initiation of anticoagulation during the first 3 months. A longer follow-up is needed, as well as computed tomography studies to detect nonobstructive thrombosis and better guide anticoagulation. The optimal duration of anticoagulation remains to be defined and may be longer than 3 months.

What are the remaining challenges concerning this specific prosthesis and in TMVR in general?

Longer-term FU is needed to assess the timing and mode of deterioration of the prosthesis and to assess the possibility of less-invasive reinterventions.

New transcatheter heart valve platforms and designs are expected to be available, which will hopefully increase the feasibility of TMVR, simplify the procedure by allowing for a transseptal approach, and further reduce the periprocedural complications.

The results in the present study suggest that the evaluation of the mitral valve anatomy using multimodality imaging is improving. However, questions remain concerning the effect of the treatment of secondary MR in heart failure patients. Previous experiments, clinical observations, and the results from COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) suggest that it is essential to intervene early on the MR if medical therapy fails ***(Obadia et al., 2018; Stone et al., 2018)***. The profile of the “responders to valve intervention” is still to be refined.

More evidence is expected from new trials. A pivotal international clinical study on prosthesis will enroll #1,000 patients. It is also necessary to carry distinct evaluation between patients with secondary MR and those with primary MR who are fewer but carry specific problems. A feasibility study of the prosthesis will be performed in patients with severe mitral annular calcification.

The following step of the evaluation will be the performance of randomized clinical trials. In operable high-risk patients, the comparator should be surgical valve replacement as in the ongoing prospective APOLLO trial (NCT03242642). In inoperable patients with secondary MR who have nevertheless an acceptable life expectancy, up until now the comparator was guideline-directed medical therapy, but the excellent results obtained in COAPT in selected patients suggest considering MitraClip, when suitable, as the comparator. This evidence will allow to better determine the subset of patients who may potentially benefit from TMVR.

Overall, the results in this feasibility study of TMVR were far better than the early reports on TMVR thanks to the progresses made at every step: patient selection, procedural performance, and technology development ***(Requeiro et al., 2017)***. Thus, it seems that we are reaching "the end of the beginning," but there is still a long way to go.

Conclusions:

Transcatheter MVR is evolving into an alternative for patients with severe mitral valve disease who are poor candidates or have increased risk for conventional mitral valve surgery. This field is at an early stage, and progress will be significantly slower than the development of TAVR due to the complexity of the mitral valve anatomy and pathology. We have learned important lessons during this early experience. Important challenges exist with the currently available technology. Improved and less bulky valve designs and delivery methods may improve technical success. A better understanding of the kind of anticoagulation needed for transcatheter MVR is just beginning to develop. Optimizing the patient-selection process by using multimodality imaging tools to accurately measure the annulus size and evaluate the risk of LVOT obstruction is essential to minimize complications.

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