The Emerging Role of Transcatheter Mitral Valve Implantation in Clinical Practice

An analysis of treatment options for mitral regurgitation and how TMVI can complement and extend the therapy armamentarium for MV disease.

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Therapy algorithms for mitral valve (MV) disease have particular challenges due to the anatomic and pathophysiologic complexities of the MV. Established therapeutic options alternate between the priorities of clinical efficacy and invasiveness. To date, there is no therapy available that combines both aspects in an ideal way. Rather, it is crucial to establish tailored approaches for different pathophysiologic variations of mitral regurgitation (MR) by identifying ideal concepts from former and future therapeutic options. Besides etiology of MV disease, this concept of customization should ideally also address accompanying cardiac diseases and further comorbidities. Key components for a guideline-directed, interdisciplinary approach to MV disease include specialized heart centers that combine logistics and human resources for sophisticated diagnostics and therapies for patients with MV disease, as well as professional expertise that provides the proven correlation of case load and quality of care. Furthermore, the routine interaction of an efficient heart team—consisting at least of interventional and noninterventional cardiologists, cardiac surgeons, and cardiac anesthetists—is required. Standardized treatment algorithms with daily interdisciplinary conferences, high expertise in cardiac imaging, and routine application of a wide range of therapies for MV disease are crucial fundamental prerequisites for adequate treatment quality.

Apart from established surgical and interventional concepts for treatment of MV disease, a novel concept for MR treatment—transcatheter MV implantation (TMVI)—has attracted attention in the past few years. TMVI platforms are available for the surgical transapical approach and the endovascular transvenous-transseptal approach. Most of the experience to date has been with transapical access. This article elucidates this novel technology, including the development status and currently available TMVI systems, and presents a perspective on how TMVI could complement therapy algorithms and extend the therapy armamentarium for MV disease.

ESTABLISHED THERAPEUTIC OPTIONS FOR MR TREATMENT

According to current guidelines,[1] the recommended therapies for different entities of MR are surgery; catheter-based, endovascular, edge-to-edge therapy using MitraClip (Abbott); and optimal medical therapy accompanied by device-based heart failure therapy in patients with secondary MR. Minor experience has been gathered with another transseptal clip system (Pascal, Edwards Lifesciences)[2] and with catheter-based techniques for direct (Cardioband, Edwards Lifesciences) and indirect (Carillon, Cardiac Dimensions, Inc.) MV annuloplasty.

MV Surgery

Surgical MV repair is the gold standard for treatment of primary degenerative MR. There are reliable long-term data demonstrating the efficacy of the surgical approach for this subset of patients.[3] Also, complex pathologies (eg, Morbus Barlow with prolapse of anterior and posterior mitral leaflets) can be addressed with surgical annu-

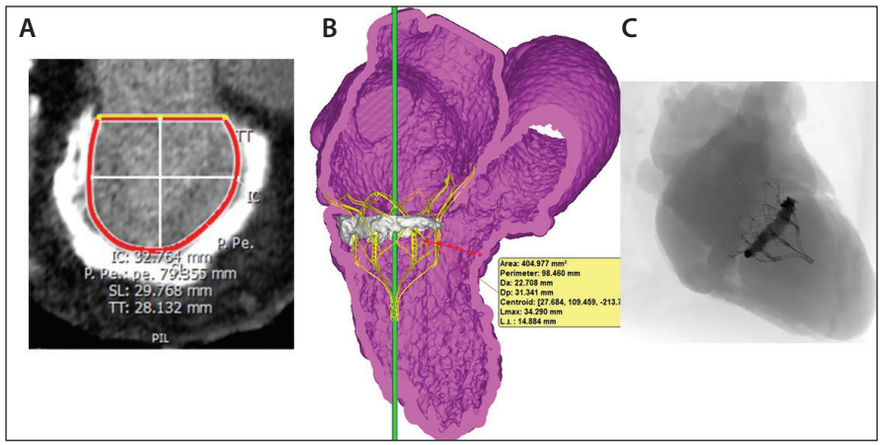

Figure 1. A crucial step for TMVI is a firm analysis of cardiac anatomy in preoperative CT. Two-dimensional evaluation of the MV annulus (A). Three-dimensional simulation of a Tendyne implantation (B) (Tendyne is a trademark of Abbott or its related companies. Reproduced with permission of Abbott, ©2020. All rights reserved. Note: Please consult Abbott.com for approval status and availability of products). Simulated angiography for visualization of optimal implant angulation (C).

loplasty and concomitant leaflet reconstruction techniques (insertion of neochordae, partial resection of the posterior mitral leaflet), with a high degree of safety and efficacy and excellent results up to 20 years.[4] In Germany, 55% of all isolated surgical MV procedures are conducted in a minimally invasive fashion via right anterolateral minithoracotomy, omitting median sternotomy.[5]

However, not all patients with significant MV disease are suitable for a surgical approach.[6] This is especially true for patients with secondary (functional) MR. Secondary MR can be caused by an alteration of the left ventricle (local or global) and an increase of the left atrial volume due to remodeling of the atrial wall (eg, because of atrial fibrillation). The ineligibility of patients with secondary MR for MV surgery is founded in the need for cardiopulmonary bypass and the often high comorbid burden in older patients. Additionally, the recurrence of significant MR subsequent to surgical MV repair due to progressive left ventricular (LV) remodeling is a well-known problem of secondary MR.[7] Nevertheless, optimal medical therapy alone in these patients is associated with high rates of heart failure rehospitalization and cardiac mortality of up to 50% after 5 years.[8]

Catheter-Based, Endovascular, Edge-to-Edge Therapy

The interventional MitraClip technique is frequently applied in this subset of patients. With a transvenous-transseptal approach, one or more nitinol clips attach to the free margins of the mitral leaflets.[9] For both primary and secondary MR, the MitraClip device has demonstrated efficacy and was incorporated in the European guidelines.[10] Furthermore, this interventional technique has high operator experience, with > 100,000 procedures conducted worldwide. The parameters for selecting the ideal MitraClip patient are paramount and subject to further discussions and investigations, especially because of the inconsistent COAPT and MITRA-FR study results.[11,12]

The advantages of catheter-based, endovascular, edge-to-edge therapy are the broad availability, high operator experience at specialized heart centers, high procedural safety profile in high-risk patients, and applicability in various MV pathologies. However, there are anatomic subsets that may cause inadequate results. For example, specific echocardiographic criteria such as reduced leaflet tissue quality with thin, short, and partially calcified leaflet portions or leaflet defects (perforations, clefts) consecutive to infective endocarditis may lead to reduced procedural efficacy. Patients with an elevated transmitral pressure gradient, degenerative MV disease with a pronounced "flail leaflet," extensive calcifications of the MV annulus, or complex Barlow disease may also have adverse results. Consequently, TMVI may be a future option in patients who are not eligible for surgical MV therapy after evaluation by a heart team due to age and/or comorbidities and are not eligible for interventional edge-to-edge therapy due to anatomic reasons.

Catheter-Based MV Implantation (TMVI)

TMVI has the potential to create a new balance between high clinical efficacy with complete resolution of significant MR and reduced invasiveness with avoidance of cardiopulmonary bypass. In 2012, the first-in-human TMVI was successfully conducted with a CardiAQ bioprosthesis (Edwards Lifesciences) by a transvenous-transseptal approach.[13] Since then, approximately 750 TMVI procedures have been conducted worldwide, most with the more direct transapical approach (Lenard Conradi, personal communication, May 2020). Lower numbers of the transvenous-transseptal approach are mainly due to the complexity of this and the high demands regarding prosthesis steerability and anchoring.

The challenges for a sophisticated TMVI system are diverse. The TMVI platform should be able to address a wide range of MV annulus dimensions. Compared with the aortic valve, the MV annulus varies strongly between patients regarding shape and size and is highly variable within the cardiac cycle for each patient. Besides adequately accurate fit for a particular annulus, the basal LV dimensions must be considered to avoid obstruction of the LV outflow tract (LVOT). Adjacent anatomic structures, such as the coronary sinus or the circumflex artery, should be not affected by the deployed bioprosthesis. Furthermore, the anchored prosthesis should be able to resist the systolic load of the cardiac cycle. Paravalvular leakage of TMVI prostheses is clinically not well tolerated, leading to hemolysis and signs of heart failure. Ideally, a TMVI system should address all varieties of primary and secondary MR. Due to a certain degree of thrombogenicity of TMVI bioprostheses, lifelong oral anticoagulation using phenprocoumon is mandatory and recommended for all available platforms.

Figures 1 and 2 provide examples of CT-based procedural planning prior to TMVI and a decision tree algorithm for suitable anatomy.

Transapical TMVI systems. To date, significant clinical experience has been gained with three TMVI systems. Results of a first implantation series using the Tendyne TMVI (Abbott) were recently published.[14] This platform consists of a 34- or 36-F transapical delivery catheter and a prosthesis built of two self-expandable nitinol frames. The outer frame is designed for placement of the valve in the MV annulus, and the inner frame has a 23- or 28-mm tricuspid, porcine, pericardial bioprosthesis. Anchoring of the valve is achieved by channeling a braided polyethylene tether through the LV apex and fixation at the apical epimyocardium using an apical pad. The prosthesis is fully repositionable at any time and fully retrievable from the LV cavity. The initial cohort, consisting of 100 high-risk patients (Society of Thoracic Surgeons [STS] score, 7.8% ± 5.7%), revealed a 30-day mortality of 6%. In 98.9% of patients predominantly with secondary MR, postoperative echocardiography documented complete elimination of MR, and 12-month follow-up showed sustained technical success with stable hemodynamics. As a result, Tendyne became the first TMVI system to receive CE Mark approval in January 2020. In April 2020, the first patients worldwide outside of study restrictions were successfully treated with the Tendyne valve for severe MR at the University Heart and Vascular Center Hamburg (UHZ) in Hamburg, Germany. The platform will be evaluated next in the three-armed North American SUMMIT study (NCT03433274). Of special interest will be a prospective randomized cohort, in which TMVI using Tendyne and catheter-based edge-to-edge therapy using MitraClip will be compared. The Tendyne platform will also be evaluated in a nonrandomized subgroup for treatment of high-risk patients presenting with mitral annular calcification. These highly complex and often severely comorbid patients have also been successfully treated at the UHZ in the past.[15]

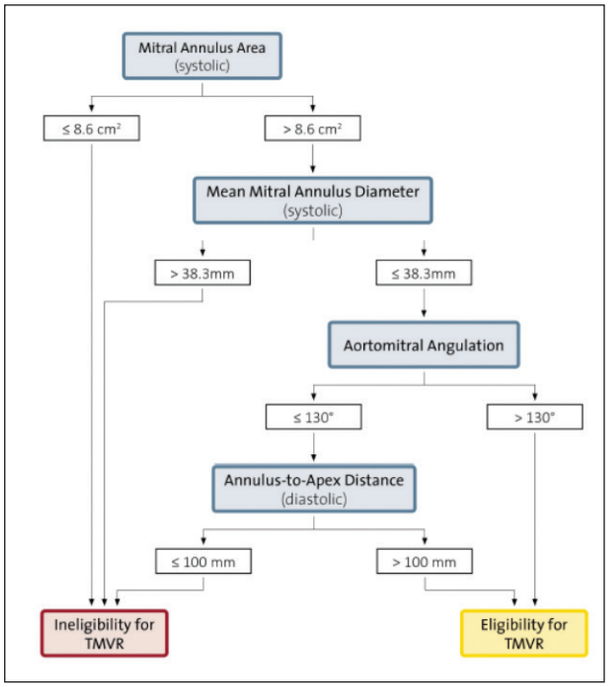

Figure 2. The most important parameters of preoperative CT in a decision tree algorithm to determine eligibility for TMVI (modified from Ludwig et al[20]).

The Intrepid TMVI system (Medtronic) consists of a 27-mm bovine, tricuspid, pericardial prosthesis, with an inner nitinol frame mounted in a 43-, 46-, or 50-mm anchoring stent. The anchoring stent serves as direct fixation to the MV anatomy with radial force using an atrial sealing skirt and small, circumferential clasps. The delivery catheter features a 35-F diameter. In 2018, the first results of a global feasibility study were published.[16] The 50 high-risk patients (mainly with secondary MR) had a mean STS score of 6.4% ± 5.5% and presented a procedural success rate of 98%, with 14% mortality at 30 days. Additionally, UHZ is participating in the APOLLO study (NCT03242642), which will compare TMVI using Intrepid versus surgical MV replacement or repair in a prospective randomized fashion.

The Tiara system (Neovasc, Inc.) consists of a self-expandable, D-shaped, nitinol frame designed to minimize interaction with the aortomitral continuity.

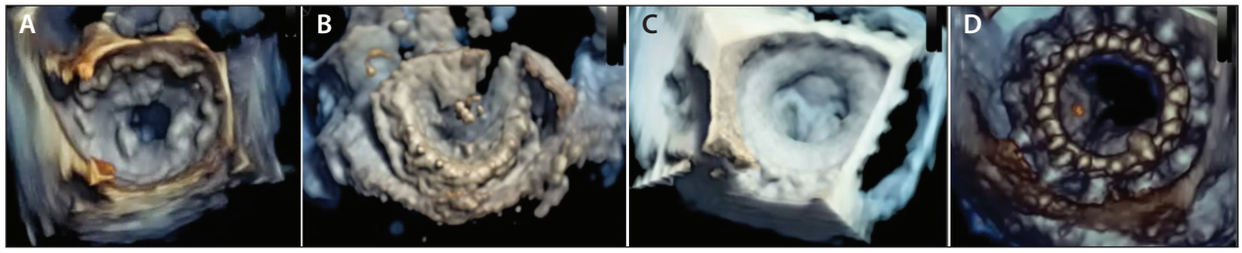

Figure 3. Postoperative 3D echocardiography ("surgeons view") after TMVI using Tendyne (A), Tiara (B), Highlife (C), and CardiAQ (D) bioprostheses.

The valve is available in 35 and 40 mm. Fixation of the prosthesis is achieved by placement of three subannular anchors; the prosthesis is deployed from atrium to ventricle, and retrieval is possible until anchor deployment. Currently, the platform is being evaluated in the TIARA-I and TIARA-II study (NCT03039855) in North America and Europe. To date, favorable results in a high-risk patient cohort (STS score, 8.4% ± 7.2%) with predominant secondary MR were documented: No case of intraprocedural death or LVOT obstruction were seen. In 93% of cases, procedural success was present, with a 30-day mortality of 11.3%.[17]

Transseptal TMVI systems. The general technical feasibility of transseptal TMVI was previously demonstrated by implanting transcatheter aortic valve implantation (TAVI) bioprostheses, originally designed for severe aortic valve stenosis, in the mitral position. In transseptal mitral valve-in-valve or valve-in-ring procedures, a transvenous approach is applied. After transseptal puncture, a TAVI heart valve is advanced and deployed in a deteriorated mitral bioprosthesis or a surgical annuloplasty ring.

For TMVI-specific systems, there is sparse documented clinical experience for this particular approach. However, there are promising platforms in the process of development and as previously mentioned, first-in-human TMVI has been successfully conducted using the transvenous-transseptal access. The CardiAQ prosthesis, which was implanted in the first-in-human case, underwent multiple design alterations. It is now called the Evoque prosthesis (Edwards Lifesciences) and is being evaluated in the North American Evoque transcatheter MV replacement early feasibility study (NCT02718001). Edwards Lifesciences is also evaluating a second TMVI platform, the Sapien M3. The Sapien M3 is an adaptation of the Sapien 3 prosthesis, which is known as a TAVI device for treating severe aortic valve stenosis. The adaptation consists of an expandable nitinol dock that interacts with the subvalvular apparatus of the native MV to create an implantation support. Published results of the initial 10 procedures documented 90% technical success, with 0% periprocedural mortality and stroke.[18] Early clinical experience is also documented for the following platforms: Cephea (Abbott),[19] MitralTech (CardioValve Ltd.; NCT03813524), HighLife (HighLife Medical, Inc.; NCT02974881), and Caisson (LivaNova PLC; NCT03661398). Postprocedural echocardiographic images of the implanted TMVI prosthesis are shown in Figure 3.

FUTURE DIRECTIONS

The maturing field of TMVI is now approaching broad clinical application in patients with severe MR. Recently, the first platform received CE Mark approval, and randomized controlled trials have been initiated to compare TMVI with established surgical and catheter-based therapies for MV disease. Depending on these study results, TMVI could complement the therapy armamentarium for MV disease. The numerous anatomic and functional challenges for TMVI have been mentioned. TMVI may be the best option for patients in whom established therapeutic strategies present obvious drawbacks. Primarily, those who are not eligible for surgery due to age and/or comorbidities or who have anatomic and/or functional parameters that exclude catheter-based, endovascular, edge-to-edge therapy can be considered for TMVI.

Currently, mainly transapical systems are applicable. In the future, transseptal systems will become available, sparing myocardial trauma and potential bleeding complications of the transapical approach. How soon this will be the case is speculative at present. However, several promising and sophisticated transseptal TMVI platforms have demonstrated technical feasibility. Nevertheless, improvements regarding catheter steerability and prosthesis anchoring must be achieved in transseptal TMVI before wider clinical application. Furthermore, future TMVI platforms must address the widest possible range of varying anatomies to avoid the main remaining limitation of current TMVI systems, which is that many patients are not considered for TMVI due to their cardiac anatomy (LV size, annulus dimensions, risk of LVOT obstruction).[20] ■

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