Chapter 22. The History of Transcatheter Mitral Valve Technology

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Over the last decade, the success of transcatheter aortic valve replacement (TAVR) has set the stage for the treatment of valvular disease with transcatheter technology. TAVR has established the basic concept that the heart valves of the *systemic circulation* can be intervened on safely and effectively. This can be done in spite of the evident risk of cerebrovascular and peripheral vascular injury as well as the prosthetic challenges with exposure to a high-pressure system generated by the left ventricle.

Several differences between the aortic and mitral valve pathophysiology and related technology are noteworthy for a better understanding of how transcatheter mitral valve therapies have evolved to date. Over the last several decades there has been a dramatic reduction in the prevalence rheumatic heart disease in developed countries. The aging of our population combined with the advent of advanced medical or interventional therapy of ischemic disease, ischemic functional secondary mitral regurgitation (MR) and degenerative primary MR in high risk patients have become the primary therapeutic target for transcatheter mitral therapy (1,2). A major difference between aortic and mitral valve therapies include several anatomic nuances and the direct link between mitral valve function and left ventricular function. Treatment of MR, particularly secondary MR, shares common ground with interventions that address causes and mediators of left ventricular (LV) function and remodeling (i.e. pharmaceutical interventions and revascularization). The importance of medical management of heart failure and left ventricular function with the interdependent relationship of mitral valve function has recently been highlighted by early results from a trial comparing best medical management against best medical management plus transcatheter mitral valve repair (TMVr) (3).

Mitral regurgitation is now the most common valve pathology. And with the shift from MS to MR over time, the requirements for therapeutic interventions in the mitral space have also changed. Transcatheter balloon valvuloplasty had historically been the sole catheter-based treatment option for stenotic mitral valves. This is in contrast to valvular regurgitation, which tends to be a more complex process necessitating a nuanced approach. Based on the different structural components that contribute to mitral valve function, methods for its restoration can be conceptualized into groups targeting: (1) leaflets & commissures; (2) annulus; (3) chordae tendineae; (4) LV, or a combination thereof. It is widely accepted and emphasized in guidelines that surgical repair is the preferred approach over replacement in primary MR because of superior outcomes (4). On the other hand, the most appropriate approach to secondary MR remains controversial in the light of recent evidence that puts the durability of surgical repair in this group of patients into question (5, 6).

Initial accounts of a transcatheter therapy for the mitral valve date back to the early 1980s, following in the footsteps of pulmonary valve interventions. In 1984, Inoue et al. first described the use of a novel balloon catheter to perform transvenous mitral commissurotomy using a trans-septal approach to intervene on the mitral valve (7). This was followed by several other reports of this approach, both in adults and children, to treat mitral stenosis and was quickly popularized thereafter. The “Inoue Balloon”

became the first mitral devices and remained the only one until more recently. Given the favorable functional outcomes and low peri-procedural risk (8), percutaneous balloon mitral valvuloplasty (PBMV) has since replaced surgical commissurotomy to a large extent and is still the primary therapeutic option recommended by current guidelines (4, 9).

With a decreasing incidence in mitral stenosis due to rheumatic heart disease and significant improvements in outcomes after open heart surgery, mitral valve disease - specifically primary MR -is now treated primarily with open surgery. The aging of the population, with a parallel increase in comorbidities, has resulted in a significant proportion of patients that are not referred for, or denied, surgery (10). This has fueled the development of new transcatheter options in order to offer a less invasive treatment options, particularly those with a high surgical risk. There are currently over 25 startup companies with devices in preclinical or clinical trials.In 2015 alone, industry invested over $2.5 billion dollars in development of transcatheter mitral valve replacement (TMVR) or TMVr options (11). Yet, TMVR and TMVr is still very much in its infancy compared to TAVR. As will be discussed in following chapters, the challenges with the development and use of transcatheter mitral options are multifaceted. Nonetheless, multiple devices have completed first-in-human implantation, started early feasibility trials or phase III clinical trials, and several have achieved Conformité Européene (CE) mark approval.

The earliest TMVr technology to be developed was the MitraClip, implanted in a human for the first time in 2003 (12). After completion of several trials in the Europe and U.S. the MitraClip gained CE mark in 2008 and commercial FDA approval in 2013. Since then it has grown its market share steadily and to date over 25,000 patients have been treated with this method worldwide and just over 4000 commercial implants have been done in the U.S (11, 13). Of note, since the clinical trial population for this device consisted of patients with primary MR, the FDA has restricted its current commercial use to inoperable patients with primary MR. But in spite of absent randomized data there has been increasing use of the MitraClip internationally for non-surgical candidates with secondary MR. The COAPT, RESHAPE HF and Mitra FR trials are currently underway to evaluate the role of the MitraClip in patients with FMR and heart failure. So far, the MitraClip has remained as the only commercially available device to directly intervene on the mitral valve leaflets.

Following in the footsteps of the MitralClip there was a number of mitral repair devices that are currently under investigation and gaining a growing experience internationally. The CARILLON is an annuloplasty device, which received its CE mark approval only one year after the MitraClip (2009). It has been implanted in several hundred patients using the coronary sinus as the placement/delivery route. Other devices that have completed the various steps of development up to CE mark approval include NeoChord (2013), Valtech Cardioband (2015) and the Mitralign device (2016).

Mitral annular anchoring, concerns with systolic anterior motion of the anterior leaflet, and navigation mitral annular calcification, are among the anatomic challenges facing TMVR development. In 2014, a conceptual milestone was reached when percutaneous implantation of a transcatheter valve in a degenerated surgical mitral valve was first reported using the Edwards Sapien XT prosthesis (14). Several sporadic reports and anecdotal evidence suggest, Sapien valves have been used occasionally to deliver a transcatheter aortic valve in the mitral position within a surgical valve, ring or in cases of severe MAC (15-17). The number of transcatheter mitral valve replacements with a dedicated mitral prosthesis and in a

native mitral valve has remained relatively small to date with less than 150 human implants worldwide. The first such replacement was successfully completed in Denmark in 2012, using the CardiAQ prosthesis. Since then, the CardiAQ device has been used in several trials in an attempt to achieve CE mark approval in Europe; but most recently a trial was stopped by Edwards Lifesciences given concerns with the design of the valve. In the U.S. there are several centers that have participated in early TMVR trials. The Tendyne experience was recently reported as part of an international feasibility trial, in which 30 patients with a high surgical risk (STS 7.3%) successfully had the transapically tethered TMVR valve implanted (18). Other valves that have entered clinical trials at various stages include the Neovasc Tiara, Medtronic Intrepid and Boston Scientific MValve devices, all competing with Tendyne to become the first commercially approved TMVR in Europe and then U.S. In addition, there is a large number of ongoing preclinical trials for several different devices (11).

Surgical mitral valve repair and replacement is associated with excellent results, even in higher-risk elderly populations, and will likely remain as the standard of care for the next decade. However, there is a mounting unmet need for patients with prohibitive surgical risk, where a less invasive option to prolong quantity and quality of life will continue to serve as a therapeutic target for the rapidly developing field of transcatheter mitral therapy.

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