Transcatheter Mitral Valve Repair or Replacement

Subjects: Cardiac & Cardiovascular Systems
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Transcatheter devices have been developed to repair or replace diseased mitral valves (MV). Transcatheter mitral valve repair (TMVr) devices have been proven to be efficient and safe, but many anatomical structures are not compatible with these technologies.

mitral regurgitation | mitral insufficiency | transcatheter mitral valve repair | transcatheter mitral valve replacement

1. Introduction

Mitral valve (MV) disease is the most common heart valve disease, with a prevalence in western countries of 1% to 2% in the general population and a prevalence of 10% in persons over 75 years of age [1]. In the last decades, rheumatic heart diseases have decreased dramatically in developed countries but, due to an aging population, the incidence of mitral regurgitation (MR) has gradually surpassed that of aortic valve stenosis, ranking first in valvular disease [1][2].

MR is a disease in which the MV does not close adequately during left ventricular systole, resulting in regurgitation of blood from the left ventricle (LV) to the left atrium, and includes primary (degenerative) MR and secondary (functional) MR [3]. Primary MR is mainly due to degenerative MV disease resulting in anatomical changes in the valve leaflets and chordal that cause MR; the recommended treatment for severe primary MR is surgery. Secondary MR is mainly due to ischemic or non-ischemic left ventricular failure with an enlarged mitral annulus, or dilatation of the left atrium in atrial fibrillation.

Optimization of pharmacological therapy is the first step in treating all patients with secondary MR, and the application of cardiac resynchronization therapy requires a comprehensive evaluation according to the relevant guidelines [4]. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines recommend either surgery (class IIa) or catheter intervention (class IIb) for patients with secondary MR who have persistent symptoms despite conventional optimal heart failure therapy [4].

In elderly patients and patients with comorbidities, the surgical risk is high and approximately 50% of patients with severe MR symptoms are not suitable candidates for open-heart surgery [5]. The morbidity and mortality rates

during hospitalization after MV repair and MV replacement in patients aged 80 to 89 years have been reported to be 6% and 13%, respectively [6]. Therefore, for elderly MR patients with comorbidities, there is an urgent need for an appropriate, less invasive treatment. The development of transcatheter mitral valve therapy offers new options for high-risk patients with MR. Many of these patients have benefited from transcatheter mitral valve repair **(TMVr)**. However, there are still patients who are anatomically unsuitable for these therapies, such as patients with a high coaptation defect or severe mitral valve calcification. As a result, interest in transcatheter mitral valve replacement (TMVR) has increased over the last few years.

2. Transcatheter Mitral Valve Repair (TMVr)

The different components of the mitral valve (leaflets, annulus, chordae, papillary muscles, and LV) and the different pathogeneses of the disease (primary and secondary) have led to a series of different therapeutic measures, such as transcatheter edge-to-edge repair (TEER), direct/indirect annuloplasty, and chordal repair. An overview of the features of transcatheter, mainly transfemoral mitral valve repair devices that have received CE make approval is indicated in **Table 1**. **Table 2** shows the clinical trials currently being conducted..

Table 1. Overview of Transcatheter Mitral Valve Repair Device Features.

Device	Repair Method	Approach	Indications	30-Day Mortality Rate
MitraClip™	TEER	transseptal	Primary/Secondary MR	0.9–6% [7][8][9][10][11][12][13]
PASCAL	TEER	transseptal	Primary/Secondary MR	1.6–2% [14][15]
Cardioband	Direct annuloplasty	transseptal	Secondary MR	3.3–5% [16][17]
Mitralign	Direct annuloplasty	transseptal	Secondary MR	4.4% [18]
Carillon	Indirect annuloplasty	transseptal	Secondary MR	1.9–2.7% [19][20][21][22]
NeoChord *	chordal repair	transapical/transeptal	Primary MR	0–1.9% [23][24]

* NeoChord is the only device which is mainly implanted transapically. TEER, transcatheter edge-to-edge repair.

Table 2. Ongoing Trial of Transcatheter Mitral Valve Repair Device.

Trial	Device	Aim
MITRA-HR RESHAPE-HF2	MitraClip	Long-term outcomes Risk stratification Patient selection

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Trial	Device	Aim
MATTERHORN REPAIR-MR		
CLASP IID/IIF	PASCAL	Safety and effectiveness compared with MitraClip
MiBAND ACTIVE	Cardioband	Post-Market approval safety and efficacy (MiBAND) Identify optimal candidates by comparing with guideline-directed medical therapy in patients with FMR (ACTIVE)
Millipede Feasibility	Millipede	Feasibility and safety
EMPOWER	Carillon	Safety and efficacy at 5 years of follow-up
Rechord	NeoChord	Safety and effectiveness compared with open surgical repair

FMR: functional mitral regurgitation.

3. Transcatheter Mitral Valve Replacement (TMVR)

MV disease is complex as well as heterogeneous, and TMVR devices are difficult to fully address all variabilities in MV anatomy and patient conditions. The development of TMVR offers a new treatment option to address MR. TMVR has many several theoretical advantages over TMVr, namely predictably reducing MR and possibly being less invasive than surgical procedures [25]. The initial TMVR clinical experience involved the following three main conditions: (1) a valve-in-valve procedure for patients with MV bioprosthesis degeneration [26][27]; (2) a valve-in-ring procedure for patients with annuloplasty rings [28][29], and (3) a valve-in-native ring procedure for patients with severe calcification of the mitral annulus [30][31]. In the case of a surgical bioprosthetic valve, some cases of annuloplasty rings, and some calcified native mitral annulus, the annular morphology offers enough support and stability to accomplish TMVR with existing valves for transcatheter aortic valve replacement (TAVR) (i.e., the Sapien valve).

Indeed, surgery is still the standard approach to MR treatment, and the transcatheter interventions for repeat procedures in patients with previous mitral surgery is highly relevant, as these patients are often at too high-risk for repeat surgery. To date, the current literature reports mitigated results and significant morbidity in some of these situations. Thus, the VIVID registry [32] reported that hemodynamics after valve-in-valve and valve-in-ring procedures were suboptimal. In particular, the 4-year mortality rate after the valve-in-ring procedure was almost 50%. The TVT registry [33] showed a 22.3% mortality rate at 1-year after valve-in-valve procedure in patients with an STS score > 8. For valve-in-mitral annular calcification (MAC) patients, the study showed that all-cause 30-day mortality was 34.5%, and 1-year all-cause mortality was 62.8% [34][35]. Strategies must thus be developed to optimize procedural results in this challenging clinical setting.

Nevertheless, since most of MR patients do not have previous surgery or significant calcification of their mitral annulus, the valved stents used for TAVR cannot be used for TMVR.

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The valve-in-valve procedure for these patients is genuine TMVR, so TMVR devices are currently in development, and the field is in constant expansion [36][37].

TMVR Devices

- Tendyne Mitral Valve System (Abbott Laboratories, IL, USA)

The Tendyne mitral valve is the only TMVR device with a CE mark (since January 2020). The Tendyne mitral valve system is a self-expanding tri-leaflet porcine pericardial valve mounted on a nitinol frame, which is fully repositionable and retrievable.

Its design has many advantages as follows: (1) the D-shaped design prevents left ventricular outflow tract obstruction (LVOTO); (2) it can be retrieved and re-released or adjusted when the implantation position or the efficacy is unsatisfactory; (3) the presence of an atrial cuff prevents perivalvular leakage; and (4) the reliance on the apical tether rather than clamping of leaflets or chordae is the most unusual feature of the Tendyne valve and the most unique in its design. The apical tether provides strong tensile force, virtually eliminating the risk of atrial embolization of the valve; secondly, there is no need to clamp the leaflets or chordae by using the apical tether because the stent on the ventricular portion can be narrowed towards the center. By adjusting the position of the tether, the valved stent can be drawn toward the free wall of the ventricle, mitigating the risk of LVOTO. The apical pad can also serve to seal the myocardial orifice created with transapical puncture. Thirteen sizes of this Tendyne valved stent are available.

The first-in-human implantation of the Tendyne valve was performed in February 2013 and was reported as a two-patient series the following year. A dramatic improvement in intracardiac pressures, along with complete elimination of MR was reported [38].

In the Tendyne global feasibility trial, one-hundred patients were enrolled in multiple centers from November 2014 to November 2017 (mean age 75.4 ± 8.1 years, secondary MR n = 89, primary MR n = 11). This prospective non-randomized study evaluated 30-day and 1-year outcomes following transapical TMVR with the Tendyne prosthesis [39].

The results demonstrated technical success in 97% of patients, and no perioperative mortality. At 30 days, 98.8% of patients presented with no or trace regurgitation. The all-cause mortality was 6% after one-month. Furthermore, the all-cause mortality was 26% with no MR in 98.4% at 1-year. A small study showed encouraging results of the Tendyne system in patients with severe MAC, for which treatment options are currently limited. The device was successfully implanted with correction of MR in nine patients; and there were no procedural deaths. One patient presented with LVOTO (valve malrotation) and required alcohol septal ablation. There was one cardiac death and one non-cardiac death in the follow-up (median 12 months). Clinical improvement with mild or no symptoms occurred in all patients alive at the end of follow-up [40].

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The SUMMIT trial (NCT03433274), is an ongoing prospective, controlled, multicenter clinical investigation with three trial cohorts: Randomized (Tendyne vs. MitraClip, 1:1 ratio), nonrandomized, and MAC, designed to evaluate the safety and effectiveness of using the Tendyne mitral valve system for the treatment of symptomatic MR. This study should offer a large dataset regarding efficacy and safety of the Tendyne system.

To date, 1000 Tendyne devices have been successfully implanted worldwide.

- Tiara TMVR System (Neovasc Inc., Richmond, BC, Canada)

The Tiara TMVR system has a self-expanding nitinol frame with three bovine pericardial leaflets. The device is D-shaped and fits geo-magnetically in the native mitral annulus. The valve features three anchors (two anterior and one posterior) on the ventricular part [41]. The ventricular anchors are designed to secure the valve (the fibrous trigone anteriorly and posterior shelf of MV annulus) which may prevent migration and reduce the risk of paravalvular leakage, LVOTO, as well as coronary ostial encroachment [41]. The valve is implanted transapically and comes in two sizes (35 mm: internal dimensions 30 × 35 mm, area 6.3–9 cm^2; 40 mm: internal dimensions 34.2 × 40 mm, area 9–12 cm^2) [42].

The first in-human implantation was reported in January 2014 [42]. The two major Tiara TMVR system trials, TIARA I (Early Feasibility Study of the Neovasc Tiara Mitral Valve System) (NCT02276547) and TIARA II (Tiara Transcatheter Mitral Valve Replacement Study) (NCT03039855), are ongoing and showed promising preliminary results in 71 patients with a 94% technical success rate and a 30-day mortality rate of 11.3 [43][44].

- Intrepid TMVR System (Medtronic, Minneapolis, MN, USA)

The Intrepid TMVR system integrates a self-expanding nitinol frame with tri-leaflet bovine pericardial valve, which includes an inner stent with valve attached and an independent conformable outer stent to engage the annulus and leaflets, providing fixation while isolating the inner stent from the dynamic anatomy [45]. The outer stent includes a flexible brim designed to aid echocardiography imaging.

Bapat et al. [46] described the implantation of the Intrepid TMVR system in the first 50 patients with a 30-day follow-up. One patient had a complication of apical hemorrhage and implantation was discontinued, while 48 of the remaining 49 patients were successfully implanted. Mortality rate at 30 days was 14%, with none to mild MR in all surviving patients. The Apollo trial (NCT03242642) began in 2017 and is expected to enroll 1350 patients. The primary endpoint is a composite of 1-year all-cause mortality, stroke, reoperation (or reintervention), and cardiovascular hospitalization rates, with estimated primary completion in October 2023 and estimated study completion in October 2028. The CE approval has not yet been granted.

- EVOQUE TMVR System (Edwards Lifesciences, Irvine, CA, USA)

The EVOQUE (Edwards Lifesciences, Irvine, CA, USA) valve is a transseptal self-expanding nitinol valve with bovine pericardial leaflets. The atrial part provides additional annular anchorage and contains a paravalvular

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sealing skirt, which is designed to minimize paravalvular leakage. Two sizes (44 and 48 mm) are currently available and are delivered via a transfemoral/transseptal approach. The delivery system allows for three planes of motion, permitting coaxial alignment and precise positioning within the annulus. To reduce the risk of LVOTO, the delivery system allows the valve to be tilted before deployment. An early feasibility trial is currently enrolling (NCT02718001). The results of the first 14 patients treated with the EVOQUE valve showed technical success in 93% of patients and one patient undergoing surgical conversion. Two patients underwent paravalvular leak closure, and one patient underwent alcohol septal ablation for LVOTO. Of the patients, 93% survived at 30-days. MR was eliminated in 80% of patients, and the remaining 20% of patients had mild MR [47].

- SAPIEN M3 system (Edwards Lifesciences, Irvine, CA, USA)

The SAPIEN M3 system is a modification of the SAPIEN 3 TAVR system, including a nitinol dock with a balloon-expandable tri-leaflet bovine pericardial valve. The SAPIEN M3 valve adds a polyethylene terephthalate (PET) skirt to minimize paravalvular leakage. Early experience in 10 patients showed promising safety and efficacy, with nine successfully implanted patients with no significant adverse events [48]. Results from a recent early feasibility study (NCT03230747) demonstrated technical success in 89% of 35 patients. All-cause mortality rate was 2.9% (n = 1), with one disabling stroke at 30 days. Echocardiographic data were available for 33 of 34 patients; 88% of patients had MR ≤ 1+ [49]. The ENCIRCLE will study the safety and efficacy of the SAPIEN M3 system in 400 patients and recently started patient recruitment (NCT04153292). The estimated primary completion date is February 2024, and the estimated study completion date is February 2028.

- HighLife TMVR system (HighLife Medical, Paris, France)

The HighLife TMVR system's special component is a sub-annular implant ring that acts as a docking system. A transfemoral retrograde transaortic approach is used to place a sub-annular ring around the MV from the start to act as an anchor for the self-expanding tri-leaflet bovine pericardial valve. This design could theoretically reduce the risk of perivalvular leakage and LVOTO. The first two case of HighLife implantation in humans showed excellent early hemodynamic performance [50]. Data from the first 15 patients showed that 13 patients were successfully implanted, and two of them (13%) were switched to surgery. Thirty-day-mortality was 20%, and LVOTO occurred in one patient. There was no mild or greater MR in the successful implantations [51].

In addition to the systems mentioned above, other technologies are under development and are still in their early stages, with only a few cases being reported. Other devices under development include the NAVI System (NaviGate Cardiac Structures Inc., Lake Forest, USA); the AltaValve TMVR system (4C Medical Technologies, Inc., Maple Grove, MN, USA); the Cephea TMVR System (Cephea Valve Technologies, Abbott Inc., San Jose, CA USA).

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