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REVIEW

Transcatheter mitral valve therapies: A comprehensive review

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ABSTRACT

Less invasive approaches offer an optimal treatment option for patients with severe mitral regurgitation who is not a candidate for surgical intervention. Favorable outcomes of transcatheter aortic valve replacement have produced great interest in the development of novel minimally invasive transcatheter technologies for repair and replacement of the mitral valve. In this review we aimed to provide an overview of the current transcatheter technologies used to treat mitral regurgitation and help clinicians in selecting the optimal therapy for their patients. We also wanted to provoke clinicians and researchers on how these technologies could be further developed in the future.

Keywords: Mitral regurgitation, mitral annuloplasties, minimally invasive surgeries

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INTRODUCTION

Valvular heart disease influences many patients worldwide and this burden will escalate further as the population ages. Mitral regurgitation (MR) is the most prevalent form of this disease, affecting around 10% of the elderly population [1,2]. Accordingly, the number of patients with MR requiring hospitalization or intervention is expected to rise severely in the following decades. To date, the principal opportunities for treatment of this entity are medical therapy and surgical intervention, surgery being considered the gold standard. However, surgery is contraindicated in almost 50% of patients with severe symptomatic MR due to associated comorbidities or underlying ventricular dysfunction which left many high-risk patients with an only medical treatment option. If untreated, severe MR is associated with poor outcomes which the mortality rate reaching up to 50% at 5-years follow-up. On the contrary, early intervention, performed before the occurrence of the adverse effects of long-standing volume overload on the left ventricle, may have result in excellent long-term outcomes [3-7]. Thus, there is a considerable need for a less invasive approach to offer an optimal treatment option to this subset of vulnerable patients.

Favorable outcomes of transcatheter aortic valve replacement (TAVR) over the last decade have produced great interest in the development and implication of novel minimally invasive transcatheter technologies specifically designed for repair and replacement of the mitral valve. However, the anatomy and pathophysiology of the mitral valve are completely different and more complex compared to the aortic valve. The annulus, leaflets, and cords of the MV, as well as the papillary muscles and the ventricle itself, make up this dynamic system. Its operation is reliant on the ventricular function as well as leaflet apposition and coaptation [8]. Thus, the engineering process behind mitral transcatheter technologies is relatively slow compared to the TAVI approach. Nevertheless, transcatheter technologies to treat MR are evolving and there are many studies ongoing that investigating the safety and efficacy of these technologies. These technologies mainly focus on devices used for leaflet repair, annular reduction, chordal implantation, and valve replacement [5,9]. Current transcatheter mitral valve devices which are in use or under clinical evaluation can be seen in Tables 1 and 2, respectively. There are also many

Table 1. Transcatheter mitral valve repair technologies

Transcatheter repair device	Trials	Status	Outcome
Direct Leaflet Repair			
MitraClip	Everest II, ACCES-EU, TRAMI and COAPT, MITRA-FR		Guideline recommended therapy
PASCAL	CLASP IID/IIF	Enrolling	Estimated to be completed in 2028
Direct Annuloplasty			
Cardioband	EFT (In human)	Enrolling	Sustained +2 MR in 1y follow-up
Millipede IRIS	EFT (In human)	Enrolling	NA
AMEND	EFT (In human)	Enrolling	reductionof the jet area and antero-posterior diameter
Mitral Bridge	CE mark clinical trial	Enrolling	No or trace MR in 6m follow-up
Mitralign Bident System	EFT	Enrolling	NA
Coronary Sinus Annuloplasty			
Carillon Mitral Contour System	AMADEUS, TITAN		Reduction of MR and decrease of the LV size at 1m follow-up
Monarc	EFT		Reduction in MR, reduced LV dimensions, improved LV function at 1y follow-up
ATRO system	MAVERIC EU/US		Reduction of annular dimension at 1y follow-up
Synthetic Support Chords			
DS1000 System	RCT	Enrolling	Estimated to be completed in 2027
Artificial Papillary Muscle			
Mitral Butterfly	Animal study	Proof of concept	100% procedural success and no device-related events in 90d follow-up
Left Ventricular Remodeling Devices			
Coapsys annuloplasty system	RCT	Enrolling	persistent survival advantage over mitral repair in 4y follow-up
PS^3 System	EFT (In human)		Reduction of MR grade with no procedural events
Ancora Device	EFT (In human)	Enrolling	Estimated to be completed in 2024

EFT:Early feasibility trial; RCT:Randomized controlled trial; MR:Mitral regurgitation; LV:Left ventricle; NA:Not available

Table 2. Transcatheter mitral valve replacement technologies

Transcatheter replacement device	Trial	Status	Outcome
CardiAQ/EVOQUE	RELIEF EFT (In human)	Enrolling	92% procedural success and 45% mortality
CardioValve	AHEAD EFT (In human)	Enrolling	Estimated to be completed in 2022
Intrepid	APOLLO (RCT)	Enrolling	NA
Tendyne	SUMMIT (RCT)	Enrolling	NA
Sapien M3	EFT (In human)	Enrolling	88% procedural success and 2.9% mortality
Tiara	TIARA I-II	Enrolling	94% procedural success and 11.3% 30-day mortality
FORTIS	EFT	Stopped	Reports of valve thrombosis

EFT:Early feasibility trial; RCT:Randomized controlled trial; NA:Not available

interventions under evaluation to take patent for transcatheter mitral valve therapy (Table 3). Figure 1 also shows a schematic illustration of some of the repair/replacement technologies.

The aim of this review is to provide a contemporary overview of the current transcatheter technologies used to treat MR and try to guide clinicians in selecting the optimal therapy for their patients, and also to provoke clinicians and researchers on how these technologies could be further developed.

A literature search of the Medline database was performed to obtain related studies discussing

Table 3. Summary of devices under evaluation to take patent for transcatheter mitral valve therapy

Method	Patent no	Assignee	Adjusted expiration date
Transcatheter Delivery System and Method with Controlled Expansion and Contraction of Prosthetic Heart Valve	US35065610P	Medtronic	2031
Transcatheter mitral valve prosthesis	US8579964B2	Neovasc Tiara, Edwards Lifesciences Cardiaq LLC	2032
Sequentially deployed transcatheter mitral valve prosthesis	US9713529B2	Neovasc Tiara	2032
Percutaneous mitral valve replacement and sealing	EP2739214A2	Mitraltech, Cardiovalve	2032
Transcatheter prosthetic heart valve delivery device with passive trigger release	EP2563277A1	Medtronic Inc	2031
Percutaneous heart valve delivery systems	US9668859B2	California Institute of Technology CalTech	2035
Device and Method for Mitral Valve Regurgitation Treatment	US20160235529A1	Sinomed Cardiovita Technology	2034
Stented transcatheter prosthetic heart valve delivery system	CN102548508A	Medtronic	2030
Perivalvular sealing for transcatheter heart valve	US20160361163A1	Edwards Lifesciences Corp	2032
Transcatheter valve structure and methods for valve delivery	EP2538880A1	Medtronic	2031
Transcatheter heart valve with micro-anchors	US20130268066A1	Edwards Lifesciences	2028
Valve replacement systems and methods	CA2870554A1	Caisson Interventional LLC	2033

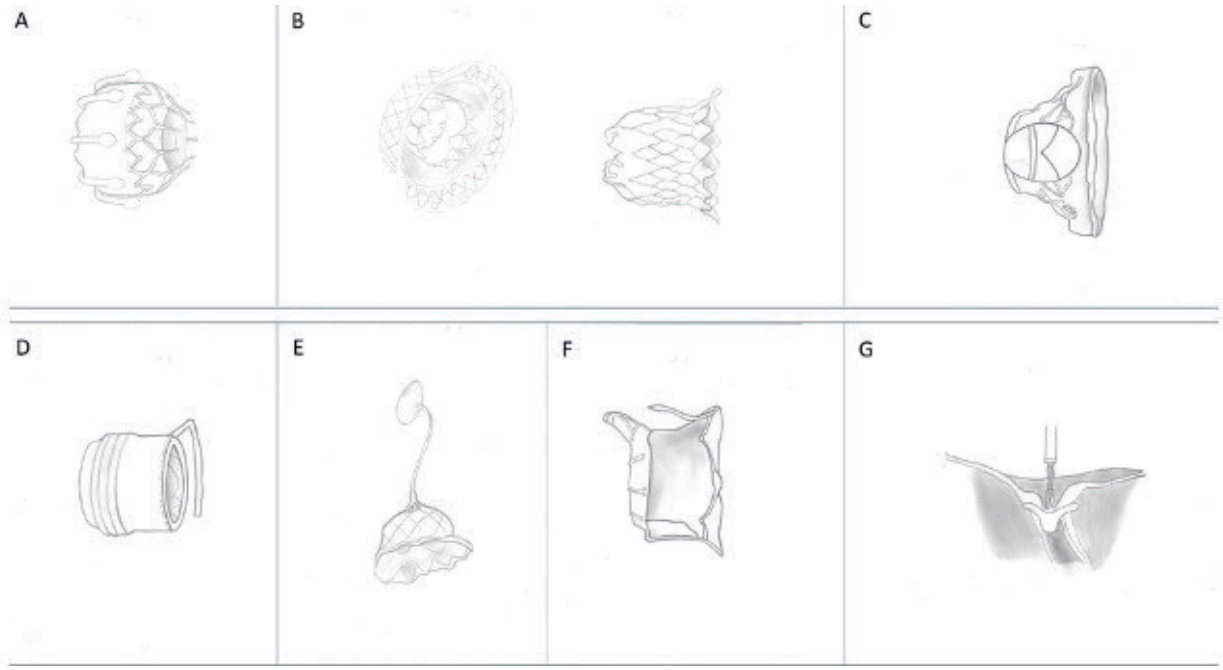

Figure 1. Schematic illustration of some mitral valve replacement/repair technologies
A:CardiAQ; B:Intrepid top/lateral view; C:CardioValve; D: Sapien M3; E: Tendyne; F: Tiara; G: MitraClip

novel transcatheter technologies and ungoing experimental studies used to treat MR. Fundamental concepts were extracted from these articles and combined appropriately. Main concepts also validated with supporting literature.

Transcatheter Repair

Direct Leaflet Repair

MitraClip (Abbott Vascular)

The MitraClip is a V-shaped polyesterdevice covered with a cobalt-chromium clip. In the first step, the clip is positioned over the regurgitation jet. Secondly, the clip arms are opened perpendicularly through the coaptation line and the device is placed into the left ventricle (LV). The leaflets are then grabbed between the clip arms as the clip is subsequently retracted. And finally, the delivery mechanism is released and the arms are closed [10]. To date, edge-to-edge leaflet repair using MitraClip is the solely guideline-recommended transcatheter treatment for MR.

EVEREST II study (randomized controlled trial) showed similar rates of death and Grade 3+ or 4+ MR at 1- and 4-year follow-up in patients who underwent MitraClip compared to surgical mitral valve replacement [11]. Both ACCESS-EU and TRAMI studies (multicenter registries) demonstrated an upgrade of NYHA functional class in patients treated for functional MR with MitrClip at 1-year and 3-month follow-up, respectively [12,13]. COAPT trial (randomized controlled trial) also showed that the rate of all-cause hospitalization and all-cause mortality was statistically significantly less (35.8% and 29.1%, respectively) in patients who underwent this therapy compared to patients who had medical therapy alone [14]. In contrast, the MITRA-FR study, in which patients were randomly assigned to Mitraclip repair plus medical treatment or medical treatment alone demonstrated similar all-cause mortality or heart failure re-hospitalization at 1-year follow-up in both arms. Nevertheless, MitraClip succeeded in a reduction of MR to Grade 2+ or less in 92% of patients at the time of hospital discharge [15].

PASCAL (Paddle, Spacer, Clasps, Alfieri Stitch) (Edwards LifeSciences)

Similar to the MitraClip, the spacer of this device is positioned between the MV leaflets. It catches, grasps and stabilizes the leaflets. A multicenter, randomized, controlled trial (CLASP IID/IIF) was conducted to assess the PASCAL device's efficacy and safety. This randomized study is now enrolling at 57 sites and is estimated to be completed in 2028 [16].

In summary, data derived from studies regarding percutaneous edge-to-edge repair devices demonstrated that these devices are safe and potentially useful in patients with severe MR. Nevertheless, these devices may not be effective in patients with secondary MR with LV dilation, in cases in which leaflet motion is severely restricted, and if there is substantial annular calcification, or multiple jets.

Direct Annuloplasty

Cardioband (Edwards Lifesciences, CA)

Cardioband is a C-shaped polyester device. It's placed through a transfemoral route followed by the insertion of multiple stainless steel screwanchors to secure the band from trigone to trigone. Following the release of the anchors, the adjustment device is attached and slowly cinched to reduce mitral annular size under transesophageal echocardiography (TEE). The adjustment device is removed once the MR has been sufficiently reduced, and the Cardioband device is left in position. It has the potential to be used primarily and in conjunction with the edge-to-edge repair or transcatheter MV replacement devices. In the feasibility trial, early after Cardioband implantation, 93% of patients had ≤ 1+ MR. The majority of these patients also remained to have ≤ +2 MR in the 1-year follow-up [8,17].

Millipede IRIS (Boston Scientific, MA)

This device consists of an adjustable nitinol zigzag-shaped semi-rigid circumferential annular ring, screw anchors, and collars. After the ring has been expanded, it is held in a supra-annular position by the anchors at each of the inferior zigzags. The ring can be cinched by moving the collars and the size of the annulus is reduced [18]. Its first in human procedures were promising and the EFS study is currently enrolling.

AMEND (Valcare Medical, Israel)

This device is a semi-rigid D-shaped nitinol annuloplasty ring which is covered by polyethylene terephthalate fabric. it is secured onto the mitral annulus with 4 zones of anchors. Once fastened, the ring is dragged anteriorly, lowering the annulus' anterior-posterior diameter [19]. The antero-posterior diameter decreased by 20%, and the jet area was reduced by 74% in the first in-human

multicenter clinical trial. The EFS study is currently enrolling.

Mitral Bridge (HRT-Heart Repair Technologies, CA)

Mitral Bridge is a nitinol bridge with an infra-annular arch that can be implanted transeptally or transapically. It is secured to the annulus by using standard sutures. It reduces the annular dimension, restore the annular saddle form, raise the coaptation height, and thus lowers the MR. The initial clinical study demonstrated promising results at a 6-month follow-up [8,19].

Mitralign Bident System (Mitralign, MA)

Mitralign Bident system implanted directly onto the posterior annulus by placing sutured pledgets through a catheter across the aortic valve. Plication of the sutures leads to a reduction of the annulus. Its use has been described in one patient with functional MR with a resultant decrease of mitral regurgitant volume [20,21].

In general, these devices are potentially beneficial in patients with secondary MR, in which the primary mechanism is the annular dilatation. Besides, these approaches can be used as adjunct therapy to other transcatheter repair or replacement methods.

Coronary Sinus Annuloplasty

Carillon Mitral Contour System (Cardiac Dimensions, WA)

The carillon device is implanted into the deep coronary vein with 2 anchors which are linked with a curved bridge. Its efficacy has been investigated in 2 studies and the results demonstrated a reduction of MR, advance of symptoms, and quality of life measures with an additional decrease of the LV size at 1-month follow-up [22,23].

Monarc (Edwards Lifesciences, CA)

The Monarc system is a nitinol implant that consists of a distal self-expanding anchor, a springlike bridge, and a proximal self-expanding anchor. The safety and EFS study showed a reduction in MR by 1 or more grades in half of the patients, reduced LV dimensions, and improved LV ejection fraction and NYHA class at 12-month follow-up [24].

ATRO system (MVRx)

Two magnetic-tipped catheters—one in the coronary sinus and the other inserted transseptally into the left atrium—along with a septal bridge on the coronary sinus side make up this system. Application of tension to the bridge shortens the septo-lateral annular dimension [25]. The early results of the safety and EFS study demonstrated a reduction of annular dimension with the majority of patients having ≤ 2+ MR at 1-year follow-up [26].

Coronary sinus annuloplasty devices are inserted percutaneously into the CS and improve leaflet coaptation and MR indirectly by constricting the mitral annulus. The major drawback of these devices is the potential to cause coronary artery compromise.

Synthetic Support Chords

DS1000 System (NeoChord, Inc., Minnesota)

The only commercially available repair device so far is the NeoChord DS1000 system, which is now being evaluated for American Food and Drug Administration (FDA) approval. The device is performed transapically through a lateral mini-thoracotomy [27]. A randomized controlled clinical trial comparing this device with the conventional surgical repair is enrolling patients and is expected to be completed in 2027 [28]. A multicenter study showed very promising success rates, in which 97% of patients showing mild post-operative mitral regurgitation. One-year survival and freedom from composite endpoints were reported as 98% and 84%, respectively [29]. In a recent systematic review, Ahmed et al. analyzed the feasibility and outcome of NeoChord device implantation in 6 studies, including 249 patients. Operative success was reached in 96.8% of the patients with no intraoperative mortality and few (~3%) minor morbidities [30].

There are also other devices in development, that have shown promising results with good safety profiles, such as Harpoon (Edwards LifeSciences), V-Chordal (Valtech, Or Yehuda, Israel), Pipeline (Gore Medical, Flagstaff, AZ), MitralStitch (Hangzhou DeJin Medtech Co Ltd., Hangzhou China), CardioMech (Trondheim, Norway), and ChordArt™ (CoreMedic AG, Biel, Switzerland). While Harpoon

is also placed transapically, V-chordal and Pipeline can be implanted transfemorally. ChordArt™ and Cardiomec devices can be implanted in both routes [31,32].

The prosthetic chordal support devices will hold an important place in the transcatheter treatment of MR with solid clinical evidence and many new devices that will be in the clinical practice soon. As in the other transcatheter technologies, the careful patient selection remains the paramount step of performing these devices with optimal outcomes. More importantly, the ability to perform the appropriate combination of leaflet repair, annuloplasty techniques, and ventricular devices together with chordal support devices will progressively improve long-term outcomes.

Artificial Papillary Muscle

Mitral Butterfly (Angel Valve, Vienna, Austria)

Mitral Butterfly is made of a nitinol-stent with ePTFE yarns which act as artificial chordae. It is a concept technology that can hold and capture the entire prolapsing valve leaflet which can be delivered through a transeptal or transaortic approach. A hook coupled with the ePTFE filaments extends into the ventricle and mimics the papillary muscle [31]. A recent animal study reported the procedural success as 100% with no device-related events within 90 days follow-up [33].

Left Ventricular Remodeling Devices

Coapsys annuloplasty system (Myocor, MN)

This device has two epicardial pads connected by a flexible cord. It compresses the left ventricle (LV) at the papillary muscles' level as well as the mitral annulus after being placed under echocardiographic guidance. Its efficacy has been analyzed in a randomized trial. Patients with ischemic dilated cardiomyopathy and ≥2+ functional MR undergoing coronary artery bypass grafting (CABG) randomized to either CABG/mitral valve repair or CABG/Coapsys. Intraoperative MR was reduced in 95% of patients, and 84% had MR grade ≤ 1 after implantation [34,35]. At 1-year follow-up, effect on MR grade, MR jet area, and NYHA class were all significantly improved with no reported deaths, device failures, reemergence of grade 3 or 4 MR, heart failure readmission, or valve reoperations [36]. At two years, patients who undergone the Coapsys device had an improved overall survival (87% vs. 77%, P=0.038) and greater freedom from adverse events (76% vs. 63%, P=0.022). The same study's four-year midterm follow-up data in a single randomization center also showed a persistent survival benefit of this device over repair. (74% vs. 50%, P=0.09) [21].

PS³ System (MVRx, CA)

The Percutaneous Septal Sinus Shortening device anchors a cord between the coronary sinus and the atrial septum that can be shortened and decrease the mitral annular septolateral distance. Its EFS study has been conducted on two patients, and MR grade was reduced from 3+ to 1+ with an additional decrease in the mean septal-lateral systolic dimension (31% reduction). No procedural complications were reported [37].

Ancora Device (Ancora Heart, Santa Clara, CA)

Through a transfemoral approach, the self-expanding, movable nitinol anchors are placed on the subannular LV myocardium. The device is gradually tightened to lessen the LV chamber circumference and the mitral annulus size [8]. The safety and early feasibility studies (EFS) of this device are currently enrolling and are expected to be completed in 2024.

An approach that addresses the basic problem of ventricular remodeling may be helpful both by reducing the ventricular size, which leads to improved contractility, and by bringing the bases of the papillary muscles closer which improves the leaflet coaptation. Early clinical trials mentioned above show with promising results that both MR and LV dysfunction may be improved by LV remodeling devices.

Transcatheter Mitral Valve Replacement

Although transcatheter mitral valve replacement (TMVR) may offer some advantages over transcatheter repair by providing a completer and more reproducible MR reduction with less technically demanding procedures, it may also have some consequences. Major challenges specific to TMVR include difficulty obtaining prosthesis stability, potential LV outflow tract obstruction, structural degeneration of the prosthetic valve, and the possibility of greater risk of injury with more catastrophic complications. Accordingly, designing

these devices seems more challenging compared to the transcatheter repair devices.

CardiAQ/EVOQUE (Edwards LifeSciences Inc)

CardiAQ is a trileaflet-bovine non-recapturable and self-expanding valve located on a nitinol frame. Implantion of the device is via the transapical or transfemoral route [38]. The early clinical trial showed a technical success of 92.3% and all-cause 30-day mortality of 53.8%. However, the trial was put on hold after 1 year to reevaluate the device design. The device had an effective anchoring mechanism but also had the possibility of LVOT obstruction due to its large profile. The device was redesigned in 2018 and was renamed EVOQUE. The new system provides a low profile to help to reduce procedural complications. The EFS for this valve is currently recruiting and is expected to be completed in 2024 [39,40].

CardioValve (Cardiovalve, Israel)

The Cardiovalve system involves of 2 nitinol frames (atrial and ventricular), 24 grasping legs, and a bovine pericardium valve. It is implanted through a transfemoral route and comes in 3 different sizes. First in-human cases were performed all with an excellent technical success (100%) with no LVOT obstruction or MR [8,39]. Device EFS study is currently enrolling patients with an estimated study completion date of December 2026 [41].

Intrepid (Medtronic Inc)

The intrepid device contains a dual nitinol self-expanding stent and a tri-leaflet bovine pericardial valve. Its champagne cork-like design is thought to oppose valve migration during high systolic pressures and help to prevent LVOT obstruction [39,42]. The device is delivered transapically. In its first EFS, 50 patients were enrolled in the study. The procedural success was reported as 98% with early mortality of 14%. No deaths were reported after 4 months. The second clinical trial, in which the patients were randomized 1:1 between surgery and this device, is currently recruiting with an estimated completion date of 2028 [43].

Tendyne (Abbott Inc)

The Tendyne system is a double frame, self-expanding porcine pericardial valve. It is delivered through a transapical route and held in the LV apex. It also has an atrial cuff which prevents the valve from entering the ventricle when the tether is under tension and perivalvular leak (PVL). Another advantage of this device is that it can be fully retrieved after surgery, if necessary [44]. Its EFS showed a procedural success rate of 96%. The 30-day mortality rate was 6% and the 1-year survival free of all-cause mortality was 72.4%. At 1 year follow-up, the majority of the patients were NYHA class I/II, and significant improvements in 6-min walk distance and quality-of-life measures were noted [45]. Currently, another trial is ongoing, actively enrolling patients, and is estimated to be completed in 2026 [46].

Sapien M3 (Edwards Lifesciences)

The SAPIEN M3 device is an adaptation of the SAPIEN 3 system that is used for the aortic position. It consists of shape memory and a nitinol stent with a trileaflet bovine pericardial valve. It also has an addition of a polyethylene terephthalate (PET) skirt to minimize paravalvular leakage and an additional shape memory nitinol dock which helps to seal the valve into place.

In the EFS including 15 patients, the device was successfully implanted in 90% of patients. MR was reduced to ≤ trivial in all implanted patients. At 30 days, there was no stroke, myocardial infarction, rehospitalization, left ventricular outflow tract obstruction, device migration, embolization, or conversion to mitral surgery. Only one patient had recurrent regurgitation due to a paravalvular leak. No mortality was noted [47]. The outcomes of the first 35 patients treated were recently presented. All-cause mortality at 30 days was 2.9%, while the procedural success rate was 88.6%. One patient had a stroke at 30 days [48].

Tiara (Neovasc Inc, Canada)

This is a self-expanding trileaflet bovine pericardial valve that is mounted on a nitinol frame. It is implanted through the transapical approach and sits in the asymmetrical mitral annulus. Its large atrial skirt helps better seating of the device and minimizes paravalvular leak. Initial results of its EFS including 71 patients showed a 94% implant success and a 11.3% 30-day mortality rate [8]. A transfemoral version of this device is also currently under development.

FORTIS (Edwards Lifesciences, Irvine, USA)

The FORTIS is a circular cloth-covered trileaflet bovine pericardial valve mounted on a self-expanding nitinol frame. It has a non-recapturable frame consists of an atrial flange and two opposing paddles that fold out at the base. When deployed, surgeons align the paddles to the MV leaflets under TEE guidance. The first-in-human implantation of this device on 13 patients showed an implant success of 76.9% and all-cause 30-day mortality of 38.5%. At 2-year follow-up, all patients but 1 were in NYHA functional class II, and there were no cases of valve malfunction [42]. However, the clinical trial was stopped because of reports of valve thrombosis [49].

Other technologies, in addition to the ones mentioned above, are being developed with fewer cases at the time being. These devices include the HighLife valve (HighLife Medical, Paris, France), the Cephea Valve (Cephea Valve Technologies, San Jose, CA), the AltaValve (4C Medical Technologies Inc, Minnesota, USA), and the NAVI system (NaviGate Cardiac Structures Inc, Lake Forest, USA).

In summary, many devices are under development in the pool of TMVR systems. Technological improvements that lead to better device delivery systems will likely make the transseptal approach more preferable in the near future. Above all, successful development of a TMVR device requires both an understanding of the complex mitral valve mechanics and knowledge of engineering parameters like material design, product development, and fabrication. Thus, to develop a simple and safe device the collaborative effort of the technical and clinical expertise is paramount.

The success of TAVR for the treatment of aortic stenosis has accelerated the progress and development of catheter-based technologies in the industry. There's been also a lot of advancement and exciting emerging technologies in the arena of catheter - based mitral valve treatments. However, it should be kept in mind that TMVR has many more challenges to overcome when compared to TAVR, and yet the trajectory is expected to be slower. Nonetheless, current devices are showing promising results in their trials and indicating that TMVR will be an available therapeutic option in the treatment of high-risk patients with MV disease in the near future. Further development of system designs, imaging techniques, and involvement of clinicians/surgeons in the development of these technologies will potentially expedite the process.

Author contribution

Study conception and design: UK; data collection: RB and UK; analysis and interpretation of results: RB and UK; draft manuscript preparation: UK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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