

Review

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Percutaneous treatment of mitral valve disease: repair vs. replacement

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Abstract

Severe mitral regurgitation is the second leading cause of cardiac valve intervention in Europe, reaching up to 10% of people older than 75 years. The mitral valve is an anatomically complex structure in which several underlying mechanisms for its malfunction could coexist. Nonetheless, over the last years, development of new techniques and devices, improved patient selection, and dedicated imaging assessment and guidance tools seem to offer novel alternatives for percutaneous mitral valve treatment. The present review aims to provide an update of the available percutaneous techniques for patients with severe mitral regurgitation.

Keywords: Mitral regurgitation, percutaneous techniques

INTRODUCTION

Severe mitral regurgitation (MR) is the second leading cause of cardiac valve intervention in Europe, reaching up to 10% of people older than 75 years^[1]. Mitral valve (MV) surgery remains the gold standard of care for patients with symptomatic severe primary MR^[2]. However, aging, a higher incidence of comorbidities, and frailty in patients with secondary MR have made necessary the development of new minimally invasive percutaneous techniques. These techniques have improved the prognosis of untreated patients with severe MR in whom mortality rates could reach 50%^[3]. The MV is an anatomically complex structure in which several underlying mechanisms for its malfunction could coexist. This complex anatomy is probably the main reason why percutaneous management of the MV has not expanded as much as that of



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the aortic valve^[4]. Nonetheless, over the last years, development of new techniques and devices, improved patient selection, and dedicated imaging assessment and guidance tools seem to offer novel alternative for percutaneous MV treatment. The present review aims to provide an update of the available percutaneous techniques for patients with severe MR.

MITRAL VALVE ANATOMY

The MV is a complex and dynamic three-dimensional structure that allows blood inflow into the left ventricle (LV) during diastole and seals the left atrium (LA) from the LV during systole. The MV is composed by several elements: mitral annulus, mitral leaflets, and subvalvular apparatus with tendinous chords and papillary muscles^[5] [Figure 1]. For correct valve function, the integrity of these components along with LV and LA is essential: an imbalance in any of these components might lead to an incompetent, stenotic, or both valve dysfunctions^[6]. A detailed understanding of the MV is important for appropriate patient selection and percutaneous correction technique.

Mitral valve annulus

The MV annulus is a dynamic, D-shaped orifice that connects the LA, LV, and mitral leaflets. The angle between the MV annulus and aortic annulus is dynamically modified over the cardiac cycle due to the displacement of the aortic-mitral curtain. In addition, a fibrous continuity attaches the anterior leaflet of the MV with the aortic valve^[8]. Whereas the anterior mitral annulus is tightly attached to the surrounding structures, the posterior mitral annulus is not as anchored. This is why annular dilatation and calcification appear more commonly in the posterior mitral annulus, leading to inadequate leaflet coaptation and MR^[9].

Mitral valve leaflets

The MV has anterior (aortic) and posterior (mural) leaflets which are contiguous through the medial and lateral commissures. In general, the anterior leaflet is larger, longer, and thicker than the posterior leaflet, occupying one third of the annulus circumference. It is arbitrarily divided into three scallops: lateral (A1), central (A2), and medial (A3). As opposed to the anterior leaflet, the posterior leaflet is crescentic with a long circumferential base and relatively short radial length, occupying two third of the annulus circumference. The posterior leaflet is divided into lateral (P1), central (P2), and medial scallops (P3) by the presence of two indentations in its free border^[9]. The leaflets coapt over a height of 8 mm on average in systole. This “coaptation reserve” prevents the development of MR in cases of annular dilatation.

Tendinous chords

The tendinous chords originate from the papillary muscle tips and are implanted into the leaflets. Although highly variable, there are two main types of tendinous chords: primary (marginal) and secondary (basal) chords. Some differences are observed among them^[5]: primary chords are thinner than basal chords, and they are inserted into the leaflet tips, limiting extensibility to prevent leaflet prolapse, while basal chords have more extensibility and are only attached in the ventricle surface of the posterior leaflet^[10].

Papillary muscles

The anterolateral and posteromedial papillary muscles originate from LV and connect through tendinous chords to the corresponding anterior, posterior, and commissural leaflet portions. The anterolateral papillary muscles have a single head and dual blood supply from the left circumflex and left anterior descending artery. The posteromedial papillary muscles have two heads and are supplied by either the right or circumflex coronary artery based on coronary dominance. The papillary muscles, among the tendinous chords, prevent leaflets prolapse and maintain the leaflets coaptation during systole. Any alterations in ventricle geometry involve MV coaptation due to papillary muscles displacement. This might occur in cases of LV remodeling due to myocardial ischemia, translating into MV tethering and MR appearance^[11].

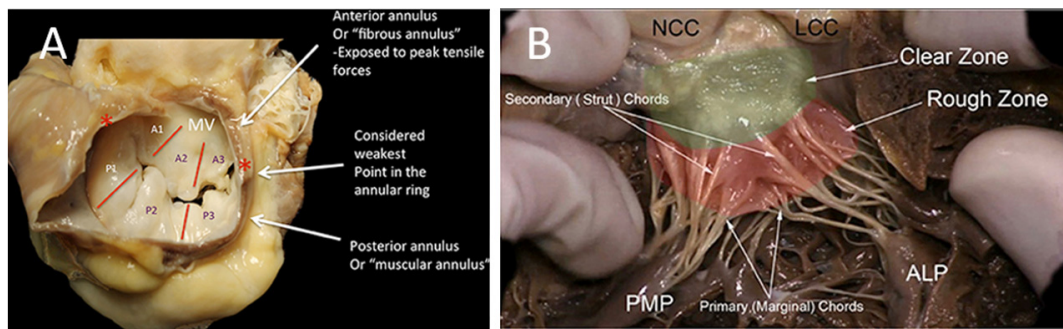


Figure 1. Mitral valve anatomy: (A) Whereas the anterior mitral annulus is tightly attached to the surrounding structures, the posterior mitral annulus is not as anchored, being the weakest point in the MV annulus. The anterior and posterior leaflets are each arbitrarily divided into three scallops: lateral (A1), central (A2), and medial (A3) and lateral (P1), central (P2), and medial (P3) scallops, respectively. (B) Subvalvular apparatus with primary and secondary tendinous chords and papillary muscles. Adapted from Pozzoli *et al.*^[7].

MITRAL REGURGITATION ETIOLOGY

Mitral regurgitation can be divided into primary or degenerative (DMR) and secondary or functional MR (FMR)^[12]. DMR is related to anatomic disorders of the MV in any of its components. These disorders lead to insufficient leaflet closure during systole. DMR may be acute and severe in some cases such as ruptured chordae or papillary muscles and infective endocarditis^[13]. The most common cause of chronic primary MR in high-income countries is mitral valve prolapse, which has a wide spectrum of etiologies and presentations. Younger populations present with severe myxomatous degeneration with gross redundancy of both anterior and posterior leaflets and the chordal apparatus (Barlow's valve). Other less common causes of DMR include connective tissue disorders, rheumatic heart disease, cleft mitral valve, and radiation heart disease^[14].

Functional MR occurs in the absence of organic MV disease; hence, the valve leaflets and chordae are structurally normal. This situation may occur due to LV wall motion abnormalities (i.e., ischemic cardiomyopathy) or LV remodeling (i.e., dilated cardiomyopathy)^[15].

Knowledge of MR mechanism cause is essential to provide specific management and treatment according to its etiology. In DMR, surgical mitral repair is the treatment of choice for symptomatic severe MR or when certain thresholds for left ventricle size, function, or both are met^[2]. However, valve intervention for FMR should only be pursued in patients with persistent symptoms and residual moderate or severe mitral regurgitation despite an adequate medical therapy^[16,17]. Initially, percutaneous approaches for MV repair or replacement were considered a feasible option only in inoperable patients with FMR^[18,19]. However, as more favorable evidence was available, 2020 ACC/AHA Valvular Heart Disease Guidelines incorporated percutaneous MV repair using MitraClip as the standard of care for FMR in patients with persistent severe symptoms (NYHA Classes II-IV) with LVEF 20%-50%, LV end-systolic diameter \leq 70 mm, and pulmonary artery systolic pressure $<$ 70 mmHg despite optimal medical treatment for LV dysfunction^[14].

MITRAL VALVE REPAIR

Leaflet repair: the edge-to-edge technique

The MitraClip® system

The MitraClip® device (Abbott Medical, Santa Clara, CA) is not only the most implemented percutaneous edge-to-edge MV repair system but also the most utilized percutaneous MV technique over the world. The device has been commercially available in Europe since 2008 and was approved by the Food and Drug

Administration in USA in 2013^[20]. The device itself consists of a polyester-covered cobalt-chromium two-armed clip [Figure 2]. The latest generation of MitraClip® (G4) has four size options: two length options of NT (short-arm) and XT (long-arm) and two width sizes of Regular and W (wide). In addition, the G4 has an independent grasping. The NT device has the following characteristics: clip length of 15 mm, grasping width of 17 mm, and arm length of 9 mm. The XT device has a longer arm compared to the NT. The XT has a closed clip length of 18 mm, a grasping width of 22 mm, and arm length of 12 mm. On the other hand, the W family is 1.5× wider than the regular clip, providing a larger grasping width for both NT and XT options. The different clip options may enable easier and quicker leaflet grasping, reduce the number of clips required, and expand percutaneous treatment to patients with less favorable anatomies^[21,22].

The EVEREST 2 trial was published more than 10 years ago and represented the most important trial for the therapy implementation at its early stage. The trial compared surgical and percutaneous MR treatment in high-risk patients, demonstrating that the MitraClip® system was safe and effective for this high-risk population. The primary effectiveness outcome at one year (intention-to-treat), defined as freedom from death, mitral valve surgery (in the percutaneous group), or reoperation (in the surgical group), or 3+ to 4+ mitral regurgitation occurred in 55% of the percutaneous group vs. 73% of the surgical group ($P = 0.007$). Rates of death were 6% vs. 6%, surgery for mitral valve dysfunction was 20% vs. 2.2%, and 3+ to 4+ mitral regurgitation was 21% vs. 20%, respectively, for percutaneous vs. surgical groups. In a per-protocol analysis, freedom from the primary outcome at one year occurred in 72% vs. 88% ($P = 0.02$), respectively. The primary effectiveness outcome at 2 years (intention-to-treat) occurred in 52% vs. 66% ($P = 0.04$), respectively. The primary effectiveness outcome at 5 years occurred in 44% vs. 64% ($P = 0.003$), respectively.

In addition, the trial defined which specific MV anatomies were more appropriate for achieving favorable results with the therapy^[23]. Nonetheless, with increasing experience, MitraClip® can be successfully implanted in patients with a more complex MV anatomy. Table 1 shows the optimal, suboptimal, and prohibitive anatomies for MV repair with the MitraClip® system and extensively with any percutaneous edge-to-edge repair system^[24].

More recently, two important randomized trials, MITRA-FR and COAPT helped to understand the treatment of patients with FMR^[25,26]. In COAPT, FMR correction with the MitraClip® system was associated with lower mortality and heart failure admissions compared to optimal medical therapy while this was not observed in MITRA-FR. Selection of patients with more severe MR and less dilated LV seemed to be the factor linked to better outcomes compared to medical therapy.

Procedure description

General anesthesia and transesophageal echocardiographic (TEE) guidance are required. The device is introduced via a 24 French orientable guiding catheter from the femoral vein through transeptal access to the left atrium. The transeptal puncture should be posterior and superior to the fossa ovalis to allow at least 3.5 cm of height to deliver the MitraClip® device adequately. Heparin is administered to achieve an activated clotting time over 250 s^[22]. The clip delivery system is advanced through the steerable guide catheter, and the clip is positioned in the site of the most severe MR jet with echocardiographic guidance. At this moment, correct orientation of the clip arms is pursued. Once optimal coaxially is achieved, the clip is then advanced inferior to the valve plane and retracted with the arms extended in order to capture the anterior and posterior MV leaflets at the location of the MR jet. The degree of MR and the measurement of trans-mitral gradients are then evaluated while the clip is in place, but before release of the device from the delivery system. If the result is correct, then the clip is released from the guide catheter^[27]. Repeat hemodynamic, angiographic, and echocardiographic assessments are performed to confirm a successful result. Additional

Table 1. Anatomical indications/restrictions for percutaneous mitral “edge-to-edge” therapies

Optimal anatomy	Suboptimal anatomy	Unsuitable anatomy
Central pathology in segment 2	Pathology in segment 1 or 3	Perforated MV leaflet or cleft
No leaflet calcification	Mild calcification outside of the grip-zone Ring calcification Post annuloplasty	Severe calcification in the grip-zone
MVOA > 4 cm ²	MVOA > 3 cm ²	MVOA < 3 cm ² , MGP ≥ 5 mmHg
Mobile length of PML ≥ 10 mm	Mobile length of PML 7-10 mm	Mobile length of PML < 7 mm
Coaptation Depth < 11 mm	Coaptation Depth ≥ 11 mm	Rheumatic leaflet thickening Restriction in systole and diastole (Carpentier IIIa)
Normal leaflet strength and mobility	Leaflet restriction in systole (Carpentier IIIb)	Barlow’s syndrome
Flail width < 15 mm	Flail width > 15 mm	
Flail gap < 10 mm		

MV: Mitral valve; MVOA: mitral valve orifice area; MGP: mean pressure gradient.

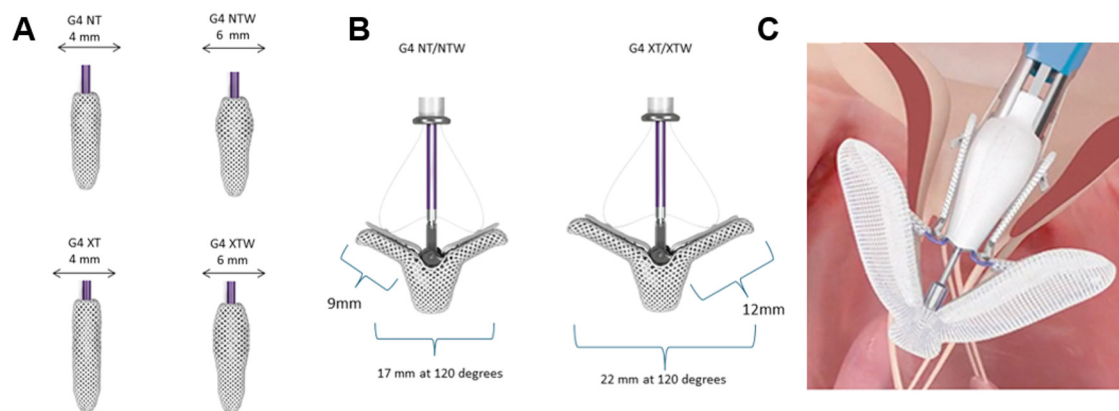


Figure 2. Edge-to-edge device: (A) four size options of MitraClip® G4 including two length sizes [NT (short-arm)/XT (long-arm)] and two width sizes [Regular/W (wide)]; (B) the W family is 1.5× wider than the regular clip offering a larger grasping width with both NT and XT options; and (C) PASCAL system. Adapted from Pozzoli *et al.*^[77].

clip implantation can be performed if necessary using the same methodology. The procedural success rate is defined as device success, which implies a reduction of MR to either optimal or acceptable levels (i.e., grade of 2+ or lower before discharge) without significant mitral stenosis and absence of major device- or procedure-related serious adverse events or any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention^[28].

Although safety is one of the main characteristics of the MitraClip® system, there might be procedural complications related to the catheterization and complications related to the device implantation. Bleeding requiring transfusion is the most common complication followed by partial clip detachment, cardiac tamponade, and new-onset atrial fibrillation^[2,15,19]. Likewise, a poor result of the intervention is the main predictor of one-year mortality. Recent reports showed an improvement in success rate and durable outcomes over time. This fact reflects the growing experience with this complex technique. Nevertheless, the mortality rate at 1 year remains high. Age, concomitant valve disease, LV ejection fraction < 30%, and associated comorbidities may also play an important role in patient outcomes^[18,21,29]. One of the main limitations of the MitraClip system is MR recurrence. This might be secondary to progression of the underlying disease or leaflet insertion loss as a result of insufficient capture of the clip in the leaflet tissue. Percutaneous reintervention is feasible, but the procedural success is markedly lower than in the index

procedure^[13].

The PASCAL® system

The Edwards PASCAL® Transcatheter Valve Repair System is a novel device based on the same principle as the MitraClip [Figure 2]. It has been designed to address some of the limitations of previous systems. It is intended to reduce the tension on the valve leaflets by introducing a 10-mm central spacer within the MV regurgitant orifice. The device is also designed to ease navigation in the LA while offering a higher degree of steerability^[21]. The CLASP study is a multicenter prospective trial of the PASCAL® system in 62 patients with significant MR despite medical therapy^[30]. Based on these promising results, the PASCAL® system gained “Conformite Europeenne” (CE) mark in early 2019. The pivotal CLASP IID/F randomized trial (NCT03706833) has begun enrollment and will compare the efficacy and safety of PASCAL® vs. MitraClip® in patients with significant DMR or FMR using a non-inferiority study design.

Annuloplasty systems

Cardioband system

Among various annuloplasty devices, percutaneous direct annuloplasty using the Cardioband system (Edwards Lifesciences Corp., Irvine, CA, USA) is a relatively new mitral valve technique very similar to conventional surgical annuloplasty rings [Figure 3]^[31]. The transeptal approach is used to deliver the device. Ring implantation is performed directly on the posterior mitral annulus under fluoroscopic and TEE guidance. Implantable metal anchors and anchor delivery shafts are mandatory for the procedure. The first anchor is deployed in the lateral commissure. Between 12 and 17 anchors are implanted using a delivery shaft. The first anchor is deployed in the lateral commissure. The anchors are fully repositionable and retrievable until deployed. Finally, the band is cinched achieving a controlled decrement in the mitral annulus dimensions with a subsequent MR reduction. The Cardioband® system received CE approbation in 2019 but is not yet available for use in USA. Currently, the Edwards Cardioband System ACTIVE Pivotal Clinical trial (NCT03016975) is ongoing to evaluate safety and effectiveness of this device in a group of patients with FMR.

A higher than expected rate of injuries during deployment of the Cardioband system has been notified. Approximately 5.7% of patients treated with Cardioband experienced coronary artery damage, most as a result of direct interaction between the anchors of the device and coronary arteries running contiguous to the valve annulus, identified either during anchor deployment or following band contraction. Preventive measures before using this system such as consistently use a guidewire in the coronary artery in order to clearly visualize vessel throughout the procedure, performing a coronary angiogram prior to first anchor deployment, verifying the proximity of the coronary artery to target anchor position throughout the procedure, and performing a final coronary angiogram before disconnecting delivery system from implant are recommended.

Carillon mitral contour system

The Carillon system is designed to treat FMR in patients with MR grades 2+ to 4+ [Figure 3]^[33]. It is a percutaneous device for mitral annuloplasty designed to reshape the anatomy and improve the function of the mitral apparatus from the coronary sinus. The device consists of two anchors connected by a shaping band. The mitral apparatus is clinched through the coronary sinus obtaining significant reduction of the regurgitant volume without affecting the valve or future treatment options. Recapture and retrieval of the device prior to release are feasible. The REDUCE FMR (CARILLON Mitral Contour System® for Reducing Functional Mitral Regurgitation) trial demonstrated a significant reduction of the mitral regurgitant volume and LV volumes in symptomatic patients with functional MR receiving optimal medical therapy. Its use was

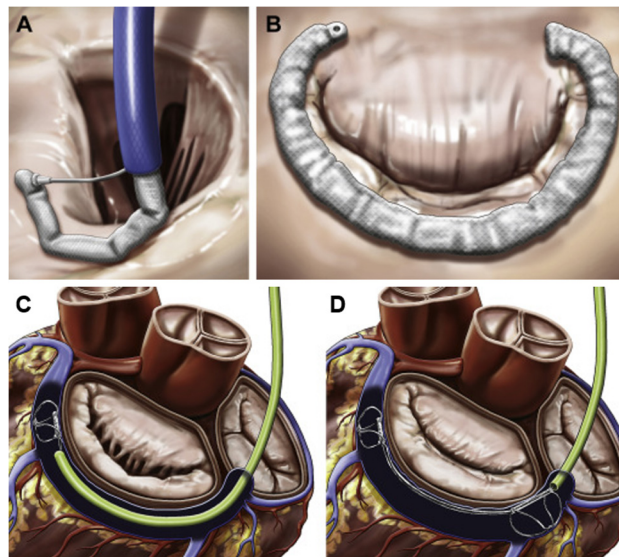


Figure 3. Annuloplasty devices system: (A, B) mitral ring annuloplasty with Cardiac Dimensions Carillon Device (Cardiac Dimension, Inc., Kirkland, Washington); and (C, D) coronary sinus annuloplasty with the Cardioband system (Edwards Lifesciences Corp., Irvine, CA, USA). Reprinted with permission from Feldman *et al.*^[32].

approved in Europe in 2011^[34], and only for research use in USA.

Chordae repair

Neochord system

Transapical off-pump mitral valve repair with neochord implantation, also known as the NeoChord procedure (Neo-Chord Inc., St. Louis Park, MN, USA), is a relatively novel option to implant artificial chords through a minimally invasive approach in patients with severe MR due to leaflet prolapse or flail. It consists of an expanded polytetrafluoroethylene synthetic fiber that is delivered via transapical access and is used as an artificial chord for mitral valve repair. After successful access is obtained, the delivery system crosses the valve and grasps onto the affected leaflet. The adequate position of the device in the affected leaflet is confirmed through data sent from the jaws of the device via fiber optic technology to a designated monitor. The delivery system then pierces the leaflet, delivering the cord and suturing it in place. The chord is thereby secured to the leaflet and then pulled and anchored to the myocardial apex site of entry. Echocardiographic guidance is used in the entire process^[35]. This device received its CE mark approval in 2012. The ReChord (Randomized Trial of the NeoChord DS1000 System Versus Open Surgical Repair) trial is a pivotal study to assess the safety and effectiveness of the device compared to open surgical repair^[36]. Its recruitment started in 2016 and is estimated to be completed by July 2027.

Transcatheter mitral valve replacement

Although percutaneous mitral repair, especially the MitraClip™ system, is the main alternative to surgery for the treatment of DMR and FMR, transcatheter MV replacement (TMVR) might confer some advantages over percutaneous repair including a potential applicability to a greater proportion of patients and a lower degree of residual mitral regurgitation^[37]. In addition, TMVR should also allow correction of valves with some degree of mitral stenosis, which is currently the most limiting factor for percutaneous MV repair.

The first TMVR in a native valve was performed in 2012^[38]. However, some challenges such as prosthesis anchoring, complete sealing (non-circular saddle-shaped dynamic annulus of large dimensions and the lack of calcified or rigid mitral annulus), interference to adjacent structures mainly the left ventricle outflow tract

Table 2. Transcatheter mitral valve replacement devices

Valves in clinical evaluation	Shape/Frame	Anchoring system	Valve position	Access
CardiaQ TMVR System (Edwards Lifesciences)	Circular, nitinol, self-expandable valve	Mitral annulus capture with native leaflet engagement	Supra-annular valve position	Transapical/transeptal access
EVOQUE TMVR System (Edwards Lifesciences)	Circular, nitinol, self-expandable valve	Mitral annulus capture with native leaflet engagement	Supra-annular valve position	Transeptal access
SAPIEN M3 System (Edwards Lifesciences)	Shape memory, nitinol, self-expandable valve	External anchor	Supra-annular valve position	Transeptal access
Cardiovalve TMVR System (Cardiovalve Ltd.)	Circular, nitinol, self-expandable valve	Mitral annulus capture with native leaflet engagement	Supra/Infra-annular position	Transseptal access
Tiara TMVR System (Neovasc Inc.)	D-shaped, nitinol, self-expandable valve	Fibrous trigone capture with native leaflet engagement	Intra-annular valve position	Transapical access
Tendyne Mitral Valve System (Abbott Laboratories)	D-shaped (outer stent) and circular (inner frame), nitinol, self-expandable valve	Apical tether	Intra-annular valve position	Transapical access
INTREPID TMVR System (Medtronic)	Circular, nitinol, double stent, self-expandable valve	Radial force and subannular cleats	Intra-annular valve position	Transeptal/Transapical access
Caisson TMVR System (LivaNova)	D-shaped, nitinol, self-expandable valve	External anchor; Mitral annulus capture with engagement at subannular fibrous groove	Supra-annular valve position	Transeptal access
HighLife TMVR System (HighLife Medical)	Circular, nitinol, self-expandable valve	External anchor; Valve in subannular mitral ring	Intra-annular valve position	Transapical access
Cephea TMVR System (Cephea Valve Technologies)	Circular, nitinol, self-expandable valve	External anchor; Valve in subannular mitral ring	Supra/Infra-annular position	Transapical/transatrial access
AltaValve TMVR System (4C Medical Technologies)	Circular, nitinol, self-expandable valve	Atrial anchoring	Supra-annular valve position	Transapical/transeptal access

(LVOT), complexity in planning the intervention, and the size/complexity in the delivery system have slowed down its development compared to transcatheter aortic valve replacement. Nonetheless, TMVR has gradually emerged as an alternative non-surgical treatment option for patients with symptomatic MV diseases who are deemed because of their high or inoperable surgical risk^[39]. Its broad spectrum of applicability in MV diseases has played a role for its implantation: from native valve mitral regurgitation to “valve in valve” in degenerated bioprosthetic valves, “valve in annuloplasty ring”, or valve in severe mitral annular calcification^[40].

Different transcatheter devices have been designed for the treatment of MR but most TMVR technologies are still in their early experience in safety and feasibility trials^[33]. Characteristics of the main TMVR devices are summarized in [Table 2](#) and [Figure 4](#)^[37,38,41-45]. In any case, some important considerations should be taken into account before planning TMVR.

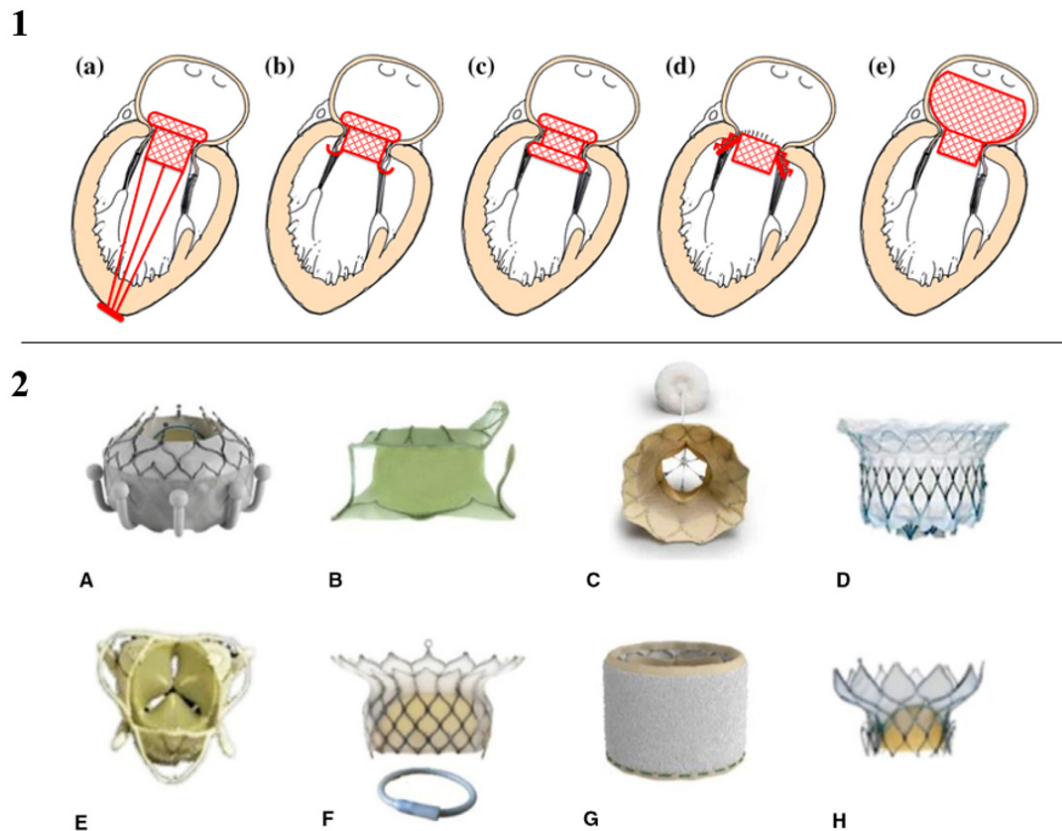


Figure 4. (1) Percutaneous mitral valve anchoring systems: (a) Atrial flange and ventricle tethers; (b) atrial flange and native valve anchors; (c) atrial and ventricle flanges; (d) subannular hooks; and (e) atrial cage. Adapted from Preston-Maher *et al.*^[46]. (2) Transcatheter mitral valve replacement devices. (A) CardiAQ/EVOQUE (Edwards Lifesciences Inc); (B) Tiara (Neovasc Inc, Canada); (C) Tendyne (Abbott Inc); (D) Intrepid (Medtronic Inc); (E) Caisson (LivaNova, UK); (F) HighLife Bioprosthesis and Subannular Implant (HighLife SAS, France); (G) SAPIEN M3 (Edwards Lifesciences Inc); and (H) Cardiovalve (Cardiovalve, Israel). Adapted from Testa *et al.*^[47].

Patients who undergo MV replacement are younger than patients who undergo aortic valve replacement^[1]. TMVR technologies are still in development and long-term data are scarce. If we extrapolate the result of surgical MV replacement, we know that bioprostheses in mitral position have higher degeneration compared to those in aortic position. Therefore, we will have to wait for ongoing clinical studies to know the real impact of degeneration^[47].

For TMVR, considering the larger dimensions of the valves and delivery system currently used, transeptal access is challenging as its limits the maneuvers and valve positioning, increasing the difficulty to deploy the mitral device^[47,48]. As a consequence, the initial experience has been obtained with a transapical or transatrial access despite being more invasive.

As described above, MV is a functional structure and primary and secondary causes might coexist. A complete evaluation of the underlying mechanism is key to deciding the most appropriate approach: repair or replacement. One major concern and potentially fatal complication of TMVR is the presence of LVOT obstruction. The LVOT is the area of the left ventricle located between the ventricle septum and the anterior mitral leaflet. LVOT obstruction is defined when there is an increment in the mean LVOT gradient ≥ 10 mmHg from baseline. The presence of a basal septal budge, calcifications of the anterior mitral leaflet, and sharp angulations between the mitral and aortic plane have been associated with this complication^[49].

Multi-slice cardiac CT is used to assess the potential for LVOT obstruction and the degree of mitral annular calcification^[50,51].

Mitral regurgitation is often coexistent with other cardiac disease, such as tricuspid regurgitation, severe pulmonary hypertension, and severe left ventricle dysfunction^[48]. Despite the increasing availability of TMVR, patients with severe mitral regurgitation may not be eligible. Niikura *et al.*^[52] showed that the ineligibility rate for TMVR is usually very high (89.0%). The most common reasons for TMVR exclusion were excessive frailty (15.3%), severe tricuspid regurgitation (15.3%), and prior aortic valve therapy (14.2%). Mitral anatomic exclusions were present in 15.8%, with severe annular calcification in 7.4%, and risk for LVOT obstruction was notably infrequent (4.4%). They showed that those patients ineligible for TMVR and treated medically have poor outcomes: cardiac death was 11.8% and death or heart failure hospitalization was 22.4% at one year. These data support the need for development of alternative management with optimal medical treatment, with the goal of improving the prognosis of these patients.

CONCLUSION

Current percutaneous mitral devices are emerging as a feasible less invasive alternative for patients with severe MR. The anatomical complexity of MV and the coexistence of various mechanisms of MR might limit the effectiveness of a unique technique for the treatment of severe MR. Along with the optimal medical therapy and the appropriate candidate selection by the heart team, the use of combined percutaneous techniques may be necessary in the future to optimize results and improve long-term outcomes. Upcoming trials are expected to address knowledge gaps, improving their safety and efficacy. The knowledge of this constantly evolving technology by clinical and interventional cardiologists might significantly improve patient outcomes.

DECLARATIONS

Authors' contributions

Article conception and design: Cepas-Guillen PL, Flores-Umanzor E, Regueiro A, Freixa X
Acquisition and analysis of bibliographic information: Cepas-Guillen PL, Flores-Umanzor E
Drafting of the manuscript: Cepas-Guillen PL, Flores-Umanzor E
Critical revision and final approval of the manuscript: Regueiro A, Freixa X

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-11. [DOI PubMed](#)
2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739-91. [DOI PubMed](#)
3. Prendergast BD, Baumgartner H, Delgado V, et al. Transcatheter heart valve interventions: Where are we? *Eur Heart J* 2019;40:422-440. [DOI PubMed](#)
4. Del Forno B, De Bonis M, Agricola E, et al. Mitral valve regurgitation: a disease with a wide spectrum of therapeutic options. *Nat Rev Cardiol* 2020;17:807-27. [DOI PubMed](#)
5. Dal-Bianco JP, Levine RA. Anatomy of the mitral valve apparatus: role of 2D and 3D echocardiography. *Cardiol Clin* 2013;31:151-64. [DOI PubMed PMC](#)
6. Zamorano JL, González-Gómez A, Lancellotti P. Mitral valve anatomy: Implications for transcatheter mitral valve interventions. *EuroIntervention* 2014;10 Suppl U:U106-11. [DOI PubMed](#)
7. Pozzoli A, Zuber M, Reisman M, Maisano F, Taramasso M. Comparative anatomy of mitral and tricuspid valve: what can the interventionist learn from the surgeon. *Front Cardiovasc Med* 2018;5:80. [DOI PubMed PMC](#)
8. Timek TA, Green GR, Tibayan FA, et al. Aorto-mitral annular dynamics. *Ann Thorac Surg* 2003;76:1944-50. [DOI PubMed](#)
9. McCarthy KP, Ring L, Rana BS. Anatomy of the mitral valve: Understanding the mitral valve complex in mitral regurgitation. *Eur J Echocardiogr* 2010;11:i3-9. [DOI PubMed](#)
10. Ritchie J, Warnock JN, Yoganathan AP. Structural characterization of the chordae tendineae in native porcine mitral valves. *Ann Thorac Surg* 2005;80:189-97. [DOI PubMed](#)
11. Otto CM. Clinical practice. Evaluation and management of chronic mitral regurgitation. *N Engl J Med* 2003;345:740-6. [DOI PubMed](#)
12. O'Gara PT, Mack MJ. Secondary mitral regurgitation. *N Engl J Med* 2020;383:1458-67. [DOI PubMed](#)
13. Estévez-Loureiro R, Benito-González T, Garrote-Coloma C, et al. Percutaneous mitral repair: current and future devices. *Ann Transl Med* 2020;8:963. [DOI PubMed PMC](#)
14. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation* 2021;143:e35-e71. [DOI PubMed](#)
15. Halim J, Van den Branden B, Coussement P, Kedhi E, Van der Heyden J. Percutaneous mitral valve repair: the necessity to redefine secondary mitral regurgitation. *Neth Heart J* 2020;28:272-9. [DOI PubMed PMC](#)
16. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med* 2014;370:23-32. [DOI PubMed PMC](#)
17. Kumar A, Al-khafaji J, Shariff M, Vaz IP, Adalja D, Doshi R. Percutaneous mitral valve repair for secondary mitral valve regurgitation: a systematic review and meta-analysis. *Eur J Intern Med* 2020;78:107-12. [DOI PubMed](#)
18. Arnold S V. Frail elderly, the ideal patients for mitralclip. *JACC Cardiovasc Interv* 2017;10:1930-1. [DOI PubMed PMC](#)
19. Metzke C, Matzik AS, Scherner M, et al. Impact of frailty on outcomes in patients undergoing percutaneous mitral valve repair. *JACC Cardiovasc Interv* 2017;10:1920-9. [DOI PubMed](#)
20. Chakravarty T, Makar M, Patel D, et al. Transcatheter edge-to-edge mitral valve repair with the mitralclip G4 system. *JACC Cardiovasc Interv* 2020;13:2402-14. [DOI PubMed](#)
21. Khan F, Winkel M, Ong G, et al. Percutaneous mitral edge-to-edge repair: state of the art and a glimpse to the future. *Front Cardiovasc Med* 2019;6:122. [DOI PubMed PMC](#)
22. Huded C, Kapadia S. Treatment of functional mitral regurgitation with transcatheter edge-to-edge repair. *Interv Cardiol Clin* 2019;8:235-43. [DOI PubMed](#)
23. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation 5-year results of EVEREST II. *J Am Coll Cardiol* 2015;66:2844-54. [DOI PubMed](#)
24. Boekstegers P, Hausleiter J, Baldus, et al. Percutaneous interventional mitral regurgitation treatment using the Mitra-Clip system. *Clin Res Cardiol* 2014;103:85-96. [DOI PubMed](#)
25. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307-18. [DOI PubMed](#)
26. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379:2297-306. [DOI PubMed](#)
27. Sherif MA, Paranskaya L, Yuecel S, et al. Mitralclip step by step; how to simplify the procedure. *Neth Heart J* 2017;25:125-30. [DOI PubMed PMC](#)
28. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions a consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol* 2015;66:308-21. [DOI PubMed](#)
29. Benito-González T, Estévez-Loureiro R, Villablanca PA, et al. Percutaneous mitral valve repair vs. stand-alone medical therapy in patients with functional mitral regurgitation and heart failure. *Cardiovasc Revasc Med* 2020;21:52-60. [DOI PubMed](#)

30. Lim DS, Kar S, Spargias K, et al. Transcatheter valve repair for patients with mitral regurgitation: 30-day results of the CLASP study. *JACC Cardiovasc Interv* 2019;12:1369-78. DOI PubMed
31. Miller M, Thourani VH, Whisenant B. The Cardioband transcatheter annular reduction system. *Ann Cardiothorac Surg* 2018;7:741-7. DOI PubMed PMC
32. Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation. *J Am Coll Cardiol* 2014;63:2057-68. DOI PubMed
33. Goode D, Dhaliwal R, Mohammadi H. Transcatheter mitral valve replacement: state of the art. *Cardiovasc Eng Technol* 2020;11:229-53. DOI PubMed
34. Witte KK, Lipiecki J, Siminiak T, et al. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Hear Fail* 2019;7:945-55. DOI PubMed
35. Di Micco L, Peruzzo P, Colli A, et al. The neochord mitral valve repair procedure: Numerical simulation of different neochords tensioning protocols. *Med Eng Phys* 2019;74:121-8. DOI PubMed
36. Randomized Trial of the Neochord™ DS1000™ System Versus Open Surgical Repair - Full Text View - ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02803957>. [Last accessed on 25 Nov 2020].
37. Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. *J Am Coll Cardiol* 2017;69:2175-92. DOI PubMed
38. Sondergaard L, De Backer O, Franzen OW, et al. First-in-human case of transfemoral cardiAQ mitral valve implantation. *Circ Cardiovasc Interv* 2015;8:e002135. DOI PubMed
39. Bapat V, Rajagopal V, Meduri C, et al. Early experience with new transcatheter mitral valve replacement. *J Am Coll Cardiol* 2018;71:12-21. DOI PubMed
40. Yoon SH, Whisenant BK, Bleiziffer S, et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. *J Am Coll Cardiol* 2017;70:1121-31. DOI PubMed
41. NAVIGATE Transcatheter Tricuspid Valve Replacement...Early Findings-Technology and Clinical Updates. Available from: <https://www.tctmd.com/slide/navigate-transcatheter-tricuspid-valve-replacement-early-findings-technology-and-clinical-0>. [Last accessed on 13 Nov 2020].
42. Cheung A, Webb J, Verheye S, et al. Short-term results of transapical transcatheter mitral valve implantation for mitral regurgitation. *J Am Coll Cardiol* 2014;64:1814-9. DOI PubMed
43. CardioValve: Device Attributes, Implant Procedure, and Early Results. Available from: <https://www.tctmd.com/slide/cardiovalve-device-attributes-implant-procedure-and-early-results>. [Last accessed on 13 Nov 2020].
44. New Technology Update: Cephea. Available from: <https://www.tctmd.com/slide/new-technology-update-cephea>. [Last accessed on 13 Nov 2020].
45. 4C Medical's AltaValve: The First Human Experience. Available from: <https://www.tctmd.com/slide/4c-medicals-altavalve-first-human-experience>. [Last accessed on 13 Nov 2020].
46. Preston-Maher GL, Torii R, Burriesci G. A technical review of minimally invasive mitral valve replacements. *Cardiovasc Eng Technol* 2015;6:174-84. DOI PubMed PMC
47. Testa L, Popolo Rubbio A, Casenghi M, Pero G, Latib A, Bedogni F. Transcatheter mitral valve replacement in the transcatheter aortic valve replacement era. *J Am Heart Assoc* 2019;8:e013352. DOI PubMed PMC
48. Overtchouk P, Piazza N, Granada J, Soliman O, Prendergast B, Modine T. Advances in transcatheter mitral and tricuspid therapies. *BMC Cardiovasc Disord* 2020;20:1. DOI PubMed PMC
49. Yoon SH, Bleiziffer S, Latib A, et al. Predictors of left ventricular outflow tract obstruction after transcatheter mitral valve replacement. *JACC Cardiovasc Interv* 2019;12:182-93. DOI PubMed
50. Coisne A, Pontana F, Tchétché D, et al. Transcatheter mitral valve replacement: Factors associated with screening success and failure. *EuroIntervention* 2019;15:E983-9. DOI PubMed
51. Vaquerizo B, Theriault-Lauzier P, Piazza N. Percutaneous transcatheter mitral valve replacement: patient-specific three-dimensional computer-based heart model and prototyping. *Rev Española Cardiol* 2015;68:1165-73. DOI PubMed
52. Niikura H, Gössl M, Kshetry V, et al. Causes and clinical outcomes of patients who are ineligible for transcatheter mitral valve replacement. *JACC Cardiovasc Interv* 2019;12:196-204. DOI PubMed