



# What Is the Next Generation of Transcatheter Mitral Valve Repair Devices?

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In the evolving scenario of the transcatheter mitral valve repair (TMVr), TMVr devices constitute a rapidly expanding field. The standard classification includes edge-to-edge repair, direct annuloplasty, indirect annuloplasty, chordal/papillary muscular repair, and the others. However, the unknowns and uncertainties to innovate a high-performing device are addressed. In this viewpoint, the authors discuss the potential future of the next generation and the challenges of TMVr devices.

**Keywords:** transcatheter mitral valve repair, transcatheter mitral valve intervention, transcatheter device, mitral regurgitation, functional mitral regurgitation

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## INTRODUCTION

Mitral regurgitation (MR) affects 9.3% of people older than 75 years, while 2.5% for aortic stenosis (1). However, transcatheter mitral intervention devices have been developed to address an unmet clinical need for inoperable patients with symptomatic severe MR. Given the more catastrophic and less forgiving complications of transcatheter mitral valve replacement, transcatheter mitral valve repair (TMVr) may be associated with a superior safety profile. Various TMVr devices are classified based on the surgical technique (Table 1), including edge-to-edge repair, direct annuloplasty, indirect annuloplasty, chordal/papillary muscular repair, and the others (2–10). Transcatheter edge-to-edge repair devices are based on Alfieri surgical technique by anchoring the free edge of the mitral leaflets and produce a double orifice. Transcatheter direct annuloplasty devices obtain reduced mitral annular dimension by anchoring mitral annulus directly, whereas, transcatheter indirect annuloplasty devices accomplish repair through adherent anatomies, such as the coronary sinus (CS) and left ventricle. Acknowledging the lack of scientific evidence to date, it is difficult to predict what the ultimate future TMVr devices will be. The purpose of this viewpoint is to address the potential future scenarios considering four aspects: safety, learning curve, the variability of disease and anatomy, and long-term outcomes.

## FAVORABLE SAFETY PROFILE

Given the complexity and the heterogeneity of mitral valve anatomy and pathology, an excellent safety profile is mandatory as a permit to be available commercially. The safety of the device is first supported by its less invasive approach. It remains an increasing and strong interest to move from a transapical procedure toward a transfemoral and transeptal procedure shown by NeoChord DS 1000 (NeoChord, Inc., St. Louis Park, MN) via transapical approach and Pipeline (Gore Medical, USA) via transfemoral approach. Second, the less interference of the mitral valve apparatus and its adjacent anatomy, the safer it is. To

**TABLE 1** | Classification of transcatheter mitral valve repair devices.

	Edge-to-edge repair	Direct annuloplasty	Indirect annuloplasty	Chordal/papillary muscular repair	Others
Transfemoral	MitraClip <sup>††</sup> Pascal <sup>†</sup>	Cardioband <sup>†</sup> Mitralign* Millipede*	Carillon <sup>†</sup> Accucinch*	Pipeline* Mitral Butterfly V-chordal	
Transapical	MitraFlex	Amend*	VenTouch* Mitraspan TASRA*	Neochord DS 1000 <sup>†</sup> Harpoon neochords* MitralStitch*	Mitra-Spacer
Others		QuantumCor (RF) Valfix	MVRx* MitralLoop Cerclage* Mitral Bridge		Mitramaze

\*In patients.

<sup>†</sup>CE mark approval.<sup>††</sup>FDA approval.**TABLE 2** | CE mark approval devices.

Device	Year of CE mark approval	No. of patients in trials	Variability of disease	Anatomical variations	Procedure duration
MitraClip	2008	In total: 4,232	FMR DMR ++++	+++	+++
PASCAL	2019	First-in-man: 23	FMR DMR ++++	+++	+++
CardioBand	2015	Early feasibility study: 31 CE trial: 61	FMR +++	+++++	+++++
Carillon	2009	AMADEUS: 48 TITAN: 36 TITAN II:36 REDUCE FMR:87	FMR +++	+	++
Mitralign	2015	Early feasibility study: 71	FMR +++	+	+++
Neochord	2012	TACT:30 TOP-MINI:49	DMR +	+	+++

+, ++, +++, +++++, ++++++ symbols represents the intensity from weak to strong.

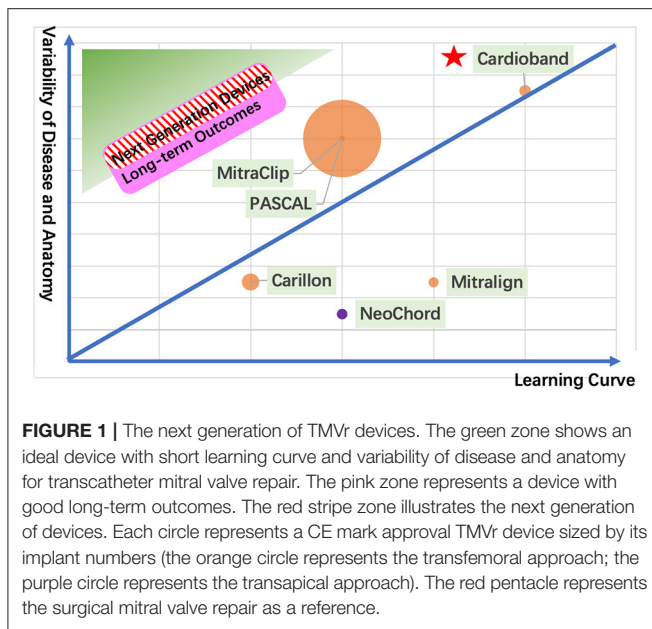
date, the most common TMVr device is the MitraClip (Abbott, Abbott Park, IL, USA) with more than 100,000 implants based on the Alfieri edge-to-edge technique with only interference of mitral leaflets. COAPT registry illustrated high freedom from device-related complications of 96.6% (11). The Carillon (Cardiac Dimension Inc., Kirkland, WA, USA) is delivered through the CS to achieve indirect mitral annuloplasty with a relatively quick procedure. However, because of the contiguity of the circumflex artery with CS, 17% of cases due to coronary artery compression were reported in the TITAN II trial (12). Additionally, its safety to reproduce the surgical technique has been confirmed as the standard therapy. Cardioband system (Edwards Lifesciences, Irvine, CA, USA) is a surgical-like direct annuloplasty applied as an isolated or adjunctive approach, waiving the possibility of increasing the severity of MR. Meanwhile, because of the pure anatomical implant, Cardioband

leaves the door open to further potential transcatheter mitral valve intervention (13). Finally, post-procedural safety matters. An ideal TMVr device does not require anticoagulation. A promising concept of transcatheter papillary muscular repair commenced, named Mitral Butterfly (AVVie, Vienna, Austria), but the thrombogenic potential of the device has not been studied clearly (14). Therefore, only CE marker-approved devices deemed with safety profiles are pooled in our further discussion (Table 2, Figure 1).

## STEEPER LEARNING CURVE

Burt et al. (15) reported that the learning curve determined the operative efficiency and long-term outcomes of surgical mitral valve repair. The impact of the operator and institutional experience can be more determinant in TMVr procedures, which were initially studied by Chhatiwalla et al. (16) in the review of the TCT Registry of 12,334 MitraClip procedures. Visual inflection points in the learning curves for acceptable

**Abbreviations:** TMVr, transcatheter mitral valve repair; MR, mitral regurgitation; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation.



procedural success were evident after ~50 cases, whereas optimal procedural success was observed in up to 200 cases. In the future, TMVr is to be considered as an alternative to surgery in eligible patients; operator experience may play a crucial role to achieve trace residual MR. With the gain of experience, the optimal procedural success and a wider spectrum of anatomical variations can increase not only in MitraClip but also in other TMVr techniques. A steep learning curve of the TMVr technique illustrates the outcomes to be less predictable in the early stage, which may prevent the promotion of the devices. Because of the lack of evidence of the learning curve for each TMVr device, the authors compared the procedure duration as the reference of the learning curve roughly (Table 2) (12, 17, 18).

## VARIABILITY OF DISEASE AND ANATOMICAL VARIATIONS

MitraClip was initially approved for organic MR and has subsequently been approved for functional MR (FMR) with a satisfactory variability of the disease. However, with the discordant clinical outcomes between COAPT and MITRA-FR trials, a notable concept of proportionate vs. disproportionate MR was applied to determine the feasibility of MitraClip, which means its variability of the disease becomes limited (11, 19). Although surgical mitral repair is the gold standard for severe degenerative MR (DMR), transcatheter edge-to-edge repair and transcatheter chordal implantation can be considered for inoperable patients with limited anatomical suitability. Concerning FMR with suboptimal surgical results and high perioperative mortality, transcatheter edge-to-edge repair and transcatheter annuloplasty play a promising and predominant role even with the lack of evidence showing the benefits of repair over replacement.

Another crucial issue is the suitability of anatomical variations of the TMVr devices, as PASCAL (Edwards Lifesciences, Irvine,

CA, USA) was developed as a central spacer and optional independent grasping to increase the anatomical suitability (20). Meanwhile, the next-generation MitraClip G4 system provides four sizes with wide clips (NTW and XTW) and narrow clips (NT and XT) with an independently grasp ability to achieve a wider spectrum of anatomical variations (21). Maisano et al. (17) compared the feasibility of other TMVr devices, considering the anatomical reasons.

## LONG-TERM OUTCOMES

Even the oldest TMVr device, MitraClip, was implanted 17 years ago for the first time. Therefore, we are still far from having unbiased evidence to compare the long-term outcomes between the TMVr devices. We can seek every new TMVr device from three stages, 30-day, 1-year, and 5-year follow-up. (1) The 30-day follow-up demonstrates the safety and feasibility of the TMVr device. Maisano et al. (17) reported the 30-day outcomes of Cardioband. The full implant success, a significant reduction in the septolateral dimension in 29 of 31 patients, and no in-hospital mortality in 1-month follow-up demonstrated the safety and feasibility of percutaneous direct mitral annuloplasty. (2) The 1-year follow-up reveals the efficacy of the TMVr device. In COAPT and MITRA-FR trials, 1-year mortalities of MitraClip were 18.8 and 24.3%, respectively (11, 19), but the clinical outcomes are discordant when comparing with the controlled cohort. Nevertheless, the concept of proportionate vs. disproportionate FMR offered us a deeper perspective to estimate the efficacy of MitraClip. (3) The 5-year follow-up ensures the durability of the TMVr device. In 5-year outcomes of the EVEREST II trial, the rates of surgery for MV dysfunction between 1- and 5-year follow-up are comparably low in either TMVr or surgical therapy, whereas the MitraClip cohort more commonly required surgery for residual MR during the 1-year follow-up (22). These outcomes convinced us of the durability of MitraClip if it is a reliable implant during the first year. Only if a device is evaluated by the staged outcomes of 30-day, 1-year, and 5-year follow-up can a satisfactory spectrum of the safety and feasibility, efficacy, and durability ensure survival.

## DISCUSSION

We provide an overview of four elements that should be taken into consideration for the next generation of TMVr devices (Table 2, Figure 1) and offer a comparison between the CE mark-approved devices. A safety profile always takes the first position for a new device. A shorter learning curve with a wider spectrum of disease and anatomy ensures the device's feasibility. Last but not least, satisfactory long-term outcomes make the TMVr device survive for a long time.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary

material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

MC: concept, design, clinical studies, and manuscript preparation. LS: manuscript review.

## REFERENCES

- Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *The Lancet*. (2006) 368:1005–11. doi: 10.1016/S0140-6736(06)69208-8
- Maisano F, Alfieri O, Banai S, Buchbinder M, Colombo A, Falk V, et al. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? *Eur Heart J*. (2015) 36:1651–9. doi: 10.1093/eurheartj/ehv123
- Fiocco A, Nadali M, Speziali G, Colli A. Transcatheter mitral valve chordal repair: current indications and future perspectives. *Front Cardiovasc Med*. (2019) 6:128. doi: 10.3389/fcvm.2019.00128
- Ali M, Shreenivas SS, Pratt DN, Lynch DR, Kereiakes DJ. Percutaneous interventions for secondary mitral regurgitation. *Circ Cardiovasc Interv*. (2020) 13:e008998. doi: 10.1161/CIRCINTERVENTIONS.120.008998
- Shah M, Jorde UP. Percutaneous mitral valve interventions (repair): current indications and future perspectives. *Front Cardiovasc Med*. (2019) 6:88. doi: 10.3389/fcvm.2019.00088
- Walther C, Fichtlscherer S, Holubec T, Vasa-Nicotera M, Arsalan M, Walther T. New developments in transcatheter therapy of mitral valve disease. *J Thorac Dis*. (2020) 12:1728–39. doi: 10.21037/jtd.2019.12.137
- Goel R, Witzel T, Dickens D, Takeda PA, Heuser RR. The QuantumCor device for treating mitral regurgitation: an animal study. *Catheter Cardiovasc Interv*. (2009) 74:43–8. doi: 10.1002/ccd.21868
- Robert PG, Ian TM. The accucinch transcatheter direct mitral valve annuloplasty system. *EuroIntervention*. (2015) 11:W60–1. doi: 10.4244/EIJV11SWA16
- Park YH, Chon MK, Lederman RJ, Sung SC, Je HG, Choo KS, et al. Mitral loop cerclage annuloplasty for secondary mitral regurgitation: first human results. *JACC Cardiovasc Interv*. (2017) 10:597–610. doi: 10.1016/j.jcin.2016.12.282
- Cerny S, Benesova M, Skalsky I, Patel NC, Subramanian VA. Persistent reduction of mitral regurgitation by implantation of a transannular mitral bridge: durability and effectiveness of the repair at 2 years—results of a prospective trial. *Eur J Cardiothorac Surg*. (2019) 55:867–73. doi: 10.1093/ejcts/ezy423
- Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. (2018) 379:2307–18. doi: 10.1056/NEJMoa1806640
- Lipiecki J, Siminiak T, Sievert H, Muller-Ehmsen J, Degen H, Wu JC, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. *Open Heart*. (2016) 3:e000411. doi: 10.1136/openhrt-2016-000411
- Pozzoli A, Gavazzoni M, Maisano F, Taramasso M. Transcatheter mitral valve replacement after transcatheter direct annuloplasty with Cardioband. *Eur Heart J*. (2020) 41:3765. doi: 10.1093/eurheartj/ehz337
- Ticar JM, Gaidulis G, Veith K, Rath C, Jarman J, Mohl W. Mitral butterfly: preclinical experience of a novel chordal repair device using an artificial papillary muscle. *JACC Basic Transl Sci*. (2020) 5:1002–14. doi: 10.1016/j.jacbts.2020.08.007
- Burt BM, ElBardissi AW, Huckman RS, Cohn LH, Cevasco MW, Rawn JD, et al. Influence of experience and the surgical learning curve on long-term patient outcomes in cardiac surgery. *J Thorac Cardiovasc Surg*. (2015) 150:1061–7.e1–3. doi: 10.1016/j.jtcvs.2015.07.068
- Chhatriwalla AK, Vemulapalli S, Szerlip M, Kodali S, Hahn RT, Saxon JT, et al. Operator experience and outcomes of transcatheter mitral valve repair in the United States. *J Am Coll Cardiol*. (2019) 74:2955–65. doi: 10.1016/j.jacc.2019.09.014
- Maisano F, Taramasso M, Nickenig G, Hammerstingl C, Vahanian A, Messika-Zeitoun D, et al. Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial. *Eur Heart J*. (2016) 37:817–25. doi: 10.1093/eurheartj/ehv603
- Chhatriwalla AK, Vemulapalli S, Holmes DR Jr, Dai D, Li Z, Ailawadi G, et al. Institutional experience with transcatheter mitral valve repair and clinical outcomes: insights from the TVT registry. *JACC Cardiovasc Interv*. (2019) 12:1342–52. doi: 10.1016/j.jcin.2019.02.039
- Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. (2018) 379:2297–306. doi: 10.1056/NEJMoa1805374
- Corpataux N, Winkel MG, Kassar M, Brugger N, Windecker S, Praz F. The PASCAL device—early experience with a leaflet approximation device: what are the benefits/limitations compared with the mitraClip? *Curr Cardiol Rep*. (2020) 22:74. doi: 10.1007/s11886-020-01305-1
- Taramasso M, Gavazzoni M, Nickenig G, Maisano F. Transcatheter mitral repair and replacement: which procedure for which patient? *EuroIntervention*. (2019) 15:867–74. doi: 10.4244/EIJ-D-19-00743
- Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, 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: 10.1016/j.jacc.2015.10.018

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