Percutaneous mitral repair: current and future devices

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Abstract: Mitral regurgitation (MR) is the second most common valvular heart disease and its prevalence is increasing with population ageing. In the recent years we have witnessed the development of several transcatheter devices to correct MR in patients at high-risk for surgery. The majority of evidence regarding safety and efficacy of this new therapy comes from MitraClip studies. However, new alternatives on the field of valve repair have emerged with promising results. The aim of this review is to portrait the landscape of transcatheter mitral repair alternatives, from currently used devices to those that will have a role in the near future.

Keywords: Percutaneous mitral valve repair; transcatheter; mitral regurgitation (MR); heart failure

Introduction

Mitral regurgitation (MR) is one of the most common symptomatic valvular disease worldwide (1). We can identify two main etiologies for MR. The degenerative MR (2-4) comprises several pathologies that involve anatomically mitral complex structures varying from simple chordal rupture (producing a scallop prolapse), to multi-segment prolapse in a valve with excess tissue and large annulus (also known as myxomatous valve). Functional MR (FMR) is secondary to LV remodeling, with left-chamber dilation and alteration of closing forces, with otherwise structurally preserved mitral structures. Significant MR is a common finding in patients with congestive heart failure (5) and is linked with an increased risk of cardiac adverse events (6-9). However, although the optimal management for FMR has still to be defined, a recent study with long follow-up has proved that medical management alone is associated with the highest rates of mortality (10). Mitral valve (MV) surgery has been the treatment of choice for severe MR if patients meet current guidelines' criteria (11). However, almost half of the patients (12,13) referred for MV surgery are not intervened, predominantly due to LV dysfunction, comorbidities or advanced age (14). Furthermore, the proportion of patients with FMR undergoing surgical treatment is even lower (15). The reason is two folds: the high-risk population and also to the fact that surgical interventions for FMR have shown an absence of prognostic benefit together with a high recurrence rate of significant MR (16-19). Likewise, FMR patients managed exclusively under medical therapy represent a high-risk population with increased rates of death and readmission due to heart failure (20). In this population catheter-based interventions have emerged to fill a large unmet need.

Device	Therapy target	CE mark year	Surgical backup	Vascular access
MITRACLIP	Leaflet coaptation	2008	Edge-to-edge Alfieri technique	Transfemoral
PASCAL	Leaflet coaptation	2010	Edge-to-edge Alfieri technique	Transfemoral
NEOCHORD	Chordae tendineae	2013	Neochord implant	Transapical
CARILLON	Indirect annuloplasty	2009	No	Transjugular
CARDIOBAND	Direct annuloplasty	2015	Flexible mitral ring	Transfemoral
MITRALIGN	Direct annuloplasty	2016	Commisuroplasty	Arterial retrograde

Figure 1 Current CE mark approved devices.

Percutaneous MV repair

The MV is an anatomical complex and its normal functioning depends on the preservation of all its components [leaflets, subvalvular apparatus, mitral annulus (MA)] and the LV normal shape. A lesion affecting any of these may lead to the development of MR (21). Several percutaneous devices have been developed, addressing different anatomical and pathophysiological targets involved in the MR genesis (22,23).

Although facing some challenges (variable degrees of MR reduction, no applicable to all anatomies, addressing only one mechanism of MR at once, challenging interaction with MV structures) MV repair still poses several advantages over replacement techniques, such as, low complication rate, less invasive approach, less anatomical foot-print, very low risk of thrombosis and infection and almost all to date available evidence. These features support the idea that MV repair will have a predominant role in the future of transcatheter mitral interventions.

Percutaneous ongoing therapies have tried to replicate the concepts of any of the already open-surgery techniques, such as edge-to-edge repair (MitraClip®, PASCAL®), ring annuloplasty (Carillon®, Cardioband®, Mitralign®, Milliepede IRIS®, Arto®, Amend®) or new chordal implantation (Neochord®). Some of them have been approved for human use and have been evaluated in clinical trials (*Figure 1*). Others are still in a very early phase and

under investigation in early feasibility studies and are beyond the scope of this review (Accucinch, Mitral loop cerclage, Pipeline, MitralBridge, ChordArt, CardioMech. MitraClamp, Mitral Butterfly, Polares, Mitra Maze, Sutra). In the next lines we will discuss the most appealing devices used so far.

Percutaneous edge-to-edge mitral valve repair (PMVR)

MitraClip®

The MitraClip® system (Abbott Vascular, IL, USA) the first device that have gained widespread clinical application, with a cumulative experience of >100,000 cases performed worldwide. This device consists of two clip arms and opposing grippers, which can be opened and closed against each other in order to grasp and gain cooptation of MV leaflets at the origin of the regurgitant jet. The procedure is usually carried out under general anesthesia and using transesophageal echo and fluoroscopic guidance. Once the device is positioned over the desired zone to treat, the system is advanced across the MV into the LV. When the device is just below the leaflets the two arms are opened and the device is retracted to capture them and subsequently closed to increase the coaptation surface of the MV leaflets. The device can be reopened and repositioned all the times necessary in order to obtain the intended result. Subsequent clips can be added as required for achieving an optimal
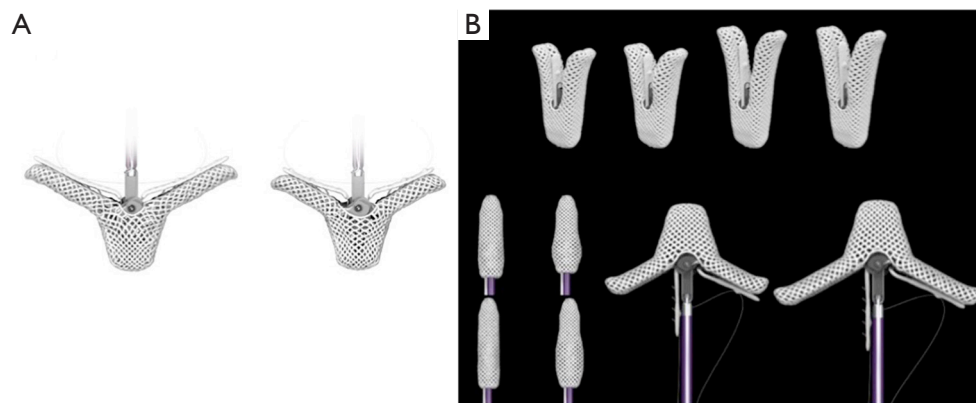
Figure 2 MitraClip device. (A) MitraClip XTR and NTR; (B) generation 4 (NTR, NTRW, XTR, XTRW). Reproduced with permission of Abbott Vascular (all rights reserved).

Table 1 Clip size selection chart

Variables	Anatomical considerations	Favored XTR	Favored NTR
Leaflet insertion	Longer leaflet	+	
	A2-P2	+	
	Large flail	+	
	Redundant leaflet	+	
	Restricted leaflet		+
Tissue quality	More than mild calcification of annulus and leaflet		+
Gradient	Smaller MV area		+
Cordial entrapment	Mitral valve commissures		+

+, preference. MV, mitral valve.

MR reduction. The amount of remainder leaflet tissue and the resulting increase in transmitral gradient are the main procedural limitations for further clip deployment. We are currently working with the 3rd generation of the device with two clip sizes available, one short (NTR) and one with long clip arms (XTR) (*Figure 2A*). Both have increased maneuverability, working length and position predictability. Information regarding their clinical use has come from the EXPAND registry, with excellent outcomes regarding MR reduction at 30 days (24) achieving MR less or equal to 1+ in almost 80% of this all-comers population. A guide to select de clip type is summarized in *Table 1*.

MitraClip® repair has proven to be a safe and effective technique in patients with either functional or degenerative MR. Early feasibility of the therapy with MitraClip® was first demonstrated in the EVEREST I trial (25) and subsequently compared with conventional surgery in the randomized controlled trial (RCT) EVEREST II (26). In these studies, very stringent echo criteria were used to select the anatomic feasibility of device implantation. However, in real world, with increasing experience, a more complex range of valve pathologies can be treated with excellent results (27).

The majority of clinical evidence in the field of percutaneous MV treatment is related to MitraClip® and it is currently the most advanced available technology for clinical use. In the EVEREST II trial, 184 patients were randomized in a 2:1 fashion to receive MitraClip® and 95 patients to undergo surgical MV treatment (repair or replacement). The device was safer than surgery with a significant reduction of major adverse events (9.6% *vs.* 57% with surgery, P<0.0001), mainly driven by a greater need for

Table 2 Main registries on MitraClip

Study	Type of study	Number of patients treated with MitraClip®	Location [number of sites]	Enrollment years	Functional MR (%)	Procedural success (MR ≤2+) (%)
Everest I	Feasibility trial	24	USA [11]	2003–2005	21	74
Everest II	RCT	184	USA [37]	2005–2008	49	77
Everest II HR	Registry	351	USA [38]	2007–2014	70.1	85.8
ACESS-EU	Registry	567	Europe [11]	2009–2011	77	91.2
MitraSwiss	Registry	100	Switzerland [4]	2009–2011	62	85
SENTINEL	Registry	628	Europe [25]	2011–2012	72	95.4
TRAMI	Registry	1,064	Germany [20]	2010–2013	71	95.2
STS/ACC TVT	Registry	564	USA [61]	2013–2014	14	93

blood transfusion in the surgical arm. Conversely, the device proved to be less efficacious. In the intent to treat analysis, survival free from the primary endpoint (death, MV surgery and MR >2+) was lower with MitraClip® as compared with surgery (55% *vs.* 73%, P=0.0007) (26). However, no differences in mortality were observed. Results of this trial at 5 years follow up confirmed the initial results of the study, with no differences in mortality or reoperation between the PMVR arm and surgery, in those patients with an initial successful repair. The proportion of patients with significant MR at 5-year follow-up was 19%, just the same observed at 1 year, reassuring the durability of the PMVR (28). Interestingly, although the proportion of patients with DMR included was greater, in the subgroup of patients with LVD and/or FMR, no differences in the primary end-point were observed between the two groups, opening a new niche for PMVR. In fact, most of the subsequent observational studies have mainly included patients with FMR (*Table 2*) (29-34). Real-world registries showed high rates of procedural success (90–95%), very low short-term adverse events and consistent improvements in symptoms, quality of life and a durable MR reduction.

However, only recently two randomized controlled trials have shed light into the controversial field of the FMR treatment. The clinical studies MITRA-FR (35) and COAPT (36) are the very first two studies that randomized patients with FMR to receive optimal medical therapy or optimal medical therapy plus edge-to-edge repair MitraClip®. The two trials showed conflicting results. In the MITRA-FR the device did not produce any benefits over the composite event of death or rehospitalizations after one year of follow-up. On the contrary, in the COAPT trial,

the device showed a significant reduction of the number of hospitalizations after 2 years of follow-up, and a reduced composite endpoint of death/rehospitalizations. It seems reasonable to try to analyze the differences between both studies in an attempt to understand these opposing findings. Main differences between trials are shown in *Table 3*.

The interesting thing about these studies is that they should be considered together and see them as complementary. We have to be cautious with patients in very advanced stages of HF (greater ventricular dilation, severe irreversible pulmonary hypertension, frequent use of inotropes), with non-severe FMR or without optimal medical therapy. If we want to replicate the positive results of COAPT, our candidates need to be in the early stages of the disease, have a significant degree of FMR [that really contributes to the clinical situation (37)], be correctly treated at the maximum tolerated drug dosages, and have good results with the device (anatomical selection and the experience of the interventional team plays a key role). Interestingly, on top of reducing major events, subanalyses of COAPT have shown that MitraClip also improves quality of life and functional class (38). We should take into account these effects when selecting patients because this may be the only therapy that will alleviate very advanced symptoms. And regarding patients with advanced HF, COAPT showed as well that MitraClip can lead to a reduction in the heart transplant or LVAD implantation rate. This finding, together with other positive data coming from registries, such as reverse remodeling, decrease in arrhythmic burden or improvement in O_2 consumption may prompt the indication in patients with LVD and advanced heart failure (36,39-42).

Table 3 Main differences between MITRA-FR and COAPT trials

Variables	MiTRA.FR (n=304)	COAPT (n=614)
Severity FMR	ESC Guidelines: ERO >20 mm^2 or RV>30 mL/beat	US Guidelines: ERO >30 mm^2 or RV>45 mL/beat
	Mean ERO 31±10 mm^2	Mean ERO 41±15 mm^2
	Mean LVEDVI 135±35 mL/m^2	Mean LVEDVI 101±34 mL/m^2
GMDT at baseline and FU	Allowing adjustment in a 'real-world fashion'	Confirmed by CEC 'maximal tolerated GMDT'. Few changes FU
AP failure	9%	5%
Procedural complications	14.5%	8.5%
MR ≤2+ 12 mo	17%	5%
Exclusion for poor clinical features	No	Severe PHT
		Right ventricular mod/sev failure
		HF stage D
		HD instability or inotropes
Hospitalizations previous year	All	≈57%

AP, acute procedural; CEC, eligibility committee; ERO, effective regurgitant orifice; FU, follow up; GDMT, guideline directed medical therapy; HD, hemodynamic instability; HF, heart failure; LVEDVI, left ventricular end-diastolic volume index; MR, mitral regurgitation; PHT, pulmonary hypertension; RV, regurgitant volume.
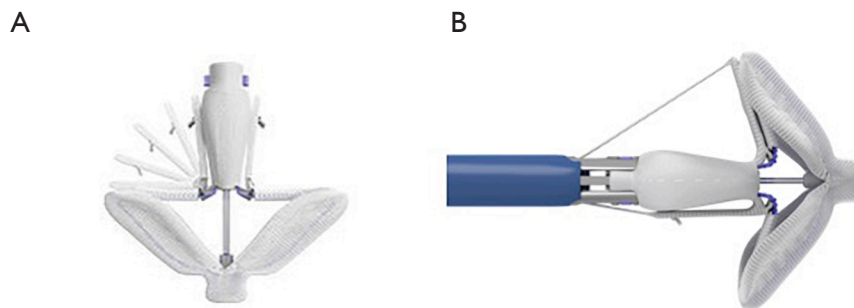
Figure 3 PASCAL device. Reproduced with permission.

Future developments

Following COAPT results it is clear that a reduction of residual MR to the minimum must be a goal with this therapy to maintain the clinical benefit. In order to achieve that standard, in a few months the Generation 4 will be available (*Figure 2B*). Main characteristics of this evolution will be the possibility of independent grasping, the availability of 4 clip sizes (the 2 NTR and XTR and the wide version of both, NTRW, XTRW), the continuous LA pressure monitoring and the easier deployment. All these features are intended to provide an easier and safer procedure, increasing the procedural success with a single clip and allowing a tailored approach for both, DMR and FMR.

PASCAL®

The PASCAL® device (Edwards Lifesciences, Irvine, California) is a transcatheter device for the transseptal leaflet repair of a leaking MV through increasing leaflet coaptation by tissue approximation with an anatomic spacer (*Figure 3*). The device is composed of 2 broad paddles, 2 clasps capable of independent movement (similar to grippers), and a nitinol woven spacer that allows improved leaflet capture, to reduce valve regurgitation while minimizing stress on the native valve leaflets. The complete system is 22 Fr and
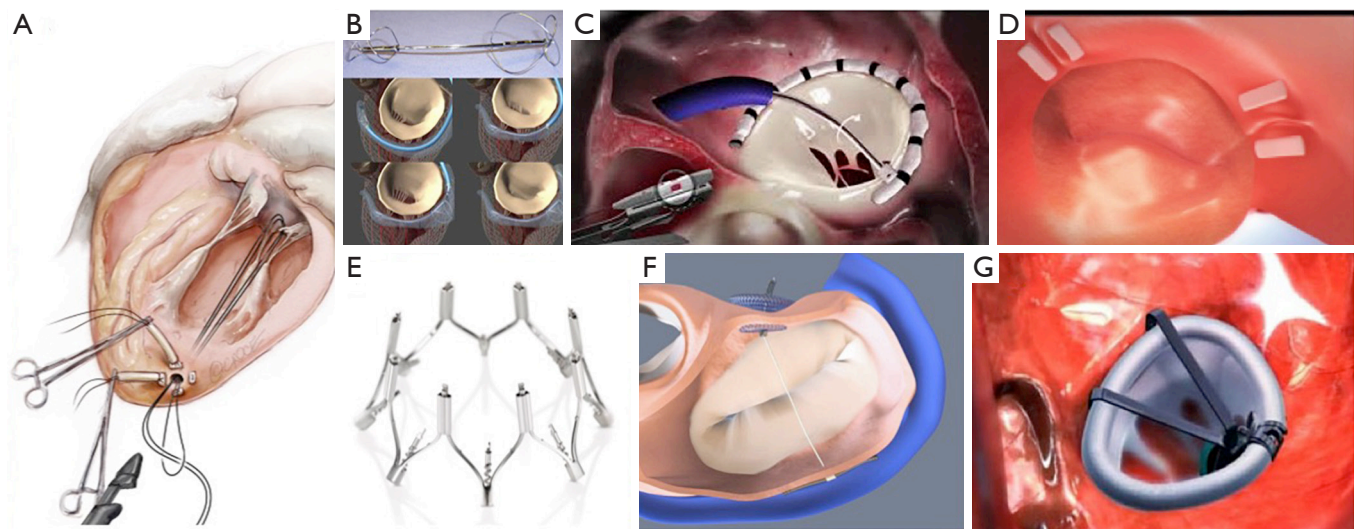
Figure 4 New devices for transcatheter mitral valve repair. (A) Carillon; (B) Cardioband; (C) Mitralign; (D) Neochord; (E) Millipede IRIS (reproduced with permission of Boston Sci.); (F) ARTO device; (G) Amend ring. Reproduced with permission.

the device can be completely elongated which favors the interaction with the subvalvular apparatus. The device has been evaluated in the CLASP registry (43). In this study 62 patients were treated with the device. MR was secondary in 56% of cases. At 30 days the MR was grade 2 or less in 98% of the patients and 85% were in functional class I-II. In addition, a significant improvement was observed in the 6-minute test and in the quality of life questionnaires. Several trials are under way with the device including direct comparisons with MitraClip in both DMR and FMR (CLASP IID/IIF Pivotal Clinical Trial, NCT03706833).

Percutaneous chordal replacement

Neochord®

Neochord® (Neochord, Minnesota, MN) are the first ePTFE chordal loops conceived to be implanted on the MV leaflets to correct flail or prolapse (*Figure 4A*) (44). Colli *et al.* reported the results of transapical implantation of Neochord in 62 patients with MV prolapse (45). Thirty-day major adverse events included 1 acute myocardial infarction (2%) and 2 cases of sepsis (3%). MR at 30 days was equal or less than 2+ in 88.7% of patients. Interestingly, a classification in 3 groups (from A-single P2 prolapse/flail- to C-para-commissural disease, annular and leaflet calcifications-) of increasing complexity has been created in order to predict device success. In the early European experience, 213 patients were included (46). The number of Type A, B and C patients

was 82 (38.5%), 98 (46%) and 33 (15.5%), respectively. Procedural success was achieved in 206 (96.7%) patients, with an in-hospital mortality of 1.9%. At 1 year, MR was severe in 7.9% with significant differences between groups (A 4%, B 9%, C 22%). This fact, together with the absence of annular treatment, underscores de importance of anatomical patient selection in order to achieve optimal results.

Transcatheter mitral valve annuloplasty (TMVA)

Annuloplasty is the most common surgical repair performed to treat MR following the 3 principles of surgical MV repair: preserve leaflet mobility, increase leaflet coaptation surface and avoid progressive annular dilation (47). This technique is widely used as a stand-alone procedure in FMR or added to leaflet repair or chordal implantation in degenerative MR (48). Some percutaneous devices have tried to reproduce undersized MV annuloplasty to address dilatation of the MA. TMVA has the potential to improve outcomes in combination with edge-to-edge repair in selected patients and to increase therapeutic alternatives in patients with anatomic ineligibility for edge-to-edge repair. Another potential advantage this approach is that it preserves the native valve anatomy, allowing the possibility for future valve implantation.

Carillon®

The coronary sinus (CS) is in close relationship with two

thirds of the MA, in close relation to the posterior MV leaflet. This was the rationale behind the first catheter-based devices that aim to create an indirect annuloplasty effect through the CS. The Carillon® Mitral Contour System (*Figure 4B*; Cardiac Dimension, Inc., Kirkland, WA, USA) obtained the CE mark in 2011. This device is implanted in the CS and reducing the septolateral diameter of the MA by post-implant device shortening (49). The procedure is carried out under fluoroscopic guidance through a jugular vein access and without general anesthesia. Nevertheless, there are some limitations that have hampered the development of this technique. First, CT imaging studies have shown that the location of the CS is no coplanar to the MA, but in a more basal position (50). Second, there have been reported serious complications, such as compression of the circumflex artery or damage of the septal conduction system (51). Finally, there is no prior surgical background for the CS approach, so the long-term results are largely unknown.

Published evidence comprised 2 observational studies and a randomized trial. In the Titan trial, only 36 of 53 patients received permanent system implantation due to transient coronary compromise (recapture of the device was carried out in those cases) (52). Mortality at 1 and 12 months in this trial were 1.9% and 22.6%. In the TITAN II trial, the implant success was achieved in 83.3% patients, and 1-month and 1-year reported mortality were 2.8% and 23 %, respectively. Both trials showed a significant reduction in MR, and clinical improvement and reverse LV remodeling in patients with FMR during 2-year follow-up. Finally, REDUCE-FMR RCT compared the device to OMT in HF subjects with FMR, in a sham-based study (53). One hundred twenty patients were allocated to the device (n=87) or medical treatment (n=33). The study showed a statistically significant reduction in mitral regurgitant volume in the treatment group compared to the control group and a significant inverse LV remodeling as well. However, no differences in clinical end-points were noted, although the trial was underpowered for such findings.

Cardioband®

Cardioband® (Edwards Lifesciences, Irvine, CA) is a transcatheter device that resembles surgical incomplete direct annuloplasty technique (*Figure 4C*). The system consists of a flexible Dacron band of different sizes delivered from a transseptal approach and implanted onto the atrial side of the MA, starting from anterolateral commissure. The band is attached in a supraannular position with multiple screws from commissure to commissure under transesophageal echo and fluoro guide. After implantation, the band length is shortened through a cinching tool in order to increase leaflet coaptation and reduce MR.

Although surgical experience with flexible incomplete rings was disappointing (54), initial clinical experiences with Cardioband® are promising (55). The CE Mark Trial enrolled high-risk subjects with symptomatic FMR and annular dilation. Early outcomes of this trial in 31 patients at 1 month showed a significant reduction in the septolateral dimension of the MA (36.8±4.8 *vs.* 29±5.5 mm, P<0.01) and an increased leaflet coaptation surface (56). Following Cardioband® shortening, MR was none or trace in 6 (21%), mild in 21 (72%) and moderate in 2 (7%) cases. No procedural mortality was noted, although in-hospital mortality was 6.5% (neither procedure- nor device-related). At 30 days, 22 of the 25 patients (88%) had MR grade ≤2+. Following results of this trial showed persistent reduction in MR (92% MR ≤2+) and improvement in functional class (77% NYHA I–II) at 24 months follow up. The results are maintained at 1-year follow-up, with persistent reduction on MR grade and in the MA dimensions and with improvement in clinical status (57).

Mitralign®

The Mitralign® (Mitralign, Inc., Tewksbury, MA, USA) is a transcatheter direct annuloplasty system that mimics the Kay-Wooler commissuroplasty (*Figure 4D*) (58). The device allows the plication of the medial and lateral aspects of the MA by deploying pairs of transannular "pledgets". The procedure is carried out from a transfemoral retrograde approach under live echo and fluoroscopic guidance. Each pledget pair is pulled together resulting in a segmental posterior annuloplasty (59). In the CE Mark Trial, the system was successfully implanted in 70.4% of 71 patients with FMR (60). No intraprocedural death occurred, but 8.9% patients experienced cardiac tamponade. Thirty-day and 6-month reported all-cause mortality were 4.4% and 12.2%, respectively. Significant improvements in clinical functional class, reduction in MA dimensions, and LV remodeling were demonstrated at 6 months. However, magnitude of MR reduction is not comparable previously described devices and remodeling of the MA is restricted to small areas, thus making this device less appealing.

Millipede®

The Millipede IRIS annuloplasty device (Millipede, Inc., Santa Rosa, CA) is a semirigid, nitinol-framed, complete

ring (*Figure 4E*). Eight helical stainless-steel anchors are preattached to the base of the ring and they are used to attach the ring to the MA. The upper part of the device has 8 sliding collars that can be manipulated individually. When put under tension, each collar draws the two adjacent helical anchors closer together and this fact allows operators to customize the final annular shape and diameter. Limited clinical experience has been achieved so far, but it can be safely delivered through transseptal approach with significant reduction in MA dimensions and the degree of MR (61). Interestingly, new iterations of the device integrate an intracardiac echo probe that allows better visualization of cardiac structures for safe anchor placement.

Arto®

The ARTO system (MVRx Inc., Belmont, CA, USA) is comprised of two anchors deployed over the lateral wall of the left atrium via the CS and in the atrial septum, connected by a tether that traverses the left atrial chamber (*Figure 4F*). The idea is to deliver a coronary sinus anchor (T-bar) and an atrial septal anchor, connected by a suture whose length can be adjusted to reduce the anteroposterior (AP) annular diameter until an acceptable reduction in MR is achieved. In the Mitral Valve Repair Clinical Trial (MAVERIC) authors presented the early phase (30 days) outcome of 11 patients that were treated with the ARTO system. Effective regurgitant orifice area decreased from 30.3 ± 11.1 to 13.5 ± 7.1 mm^2, and regurgitant volumes from 45.4 ± 15.0 to 19.5 ± 10.2 mL. The mitral annular anteroposterior diameter decreased from 45.0 ± 3.3 to 38.7 ± 3.0 mm. Regarding safety issues at 30 days, no major adverse events were reported, but one patient experienced pericardial effusion and there was one asymptomatic device dislodgment (62).

Amend®

Valcare Amend system (Valcare Medical; Israel) is a complete, semi-rigid D-shaped transcatheter annuloplasty system (*Figure 4G*). The device can be delivered through a transapical or a transseptal approach. The device is anchored first in the posterior annulus and then approaches de anterior aspect. It has been used in cases as a stand-alone therapy or in combination with Neochord or MitraClip with relevant reduction of the regurgitant jet area and in the anteroposterior diameter (63).

Transcatheter multimodal approach for MR

Cardiac surgery has taught us that combination of diverse techniques addressing different mechanisms of MR may improve long-term outcomes (48). In this sense, there has been reported the first series of device combination therapy. Recently, experiences of direct and indirect TMVA after failure of PMVR with MitraClip® have been published (64-66). MitraClip® is currently the most widespread technique focus on MV leaflets, with contrasted effective results. Nevertheless, reported recurrence of significant MR may surpass 20% at 1 year (29), when applied to an all-comers population. Notably, transcatheter mitral rings may play a role as valuable adjunct catheter-based procedures to Mitraclip® or PASCAL® (or percutaneous chordal replacement) in selected patients (such as very dilated LA and MA).

Conclusions

There is a huge technological development in the field of PMVR. Due to their clinical and anatomical advantages, these repair systems will have an important role in the treatment of MR. MitraClip is so far the most established device with the broader body of evidence. Future generation devices will help to refine and expand the transcatheter repair possibilities.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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