PERCUTANEOUS MITRAL VALVE INTERVENTIONS (REPAIR): CURRENT INDICATIONS AND FUTURE PERSPECTIVES

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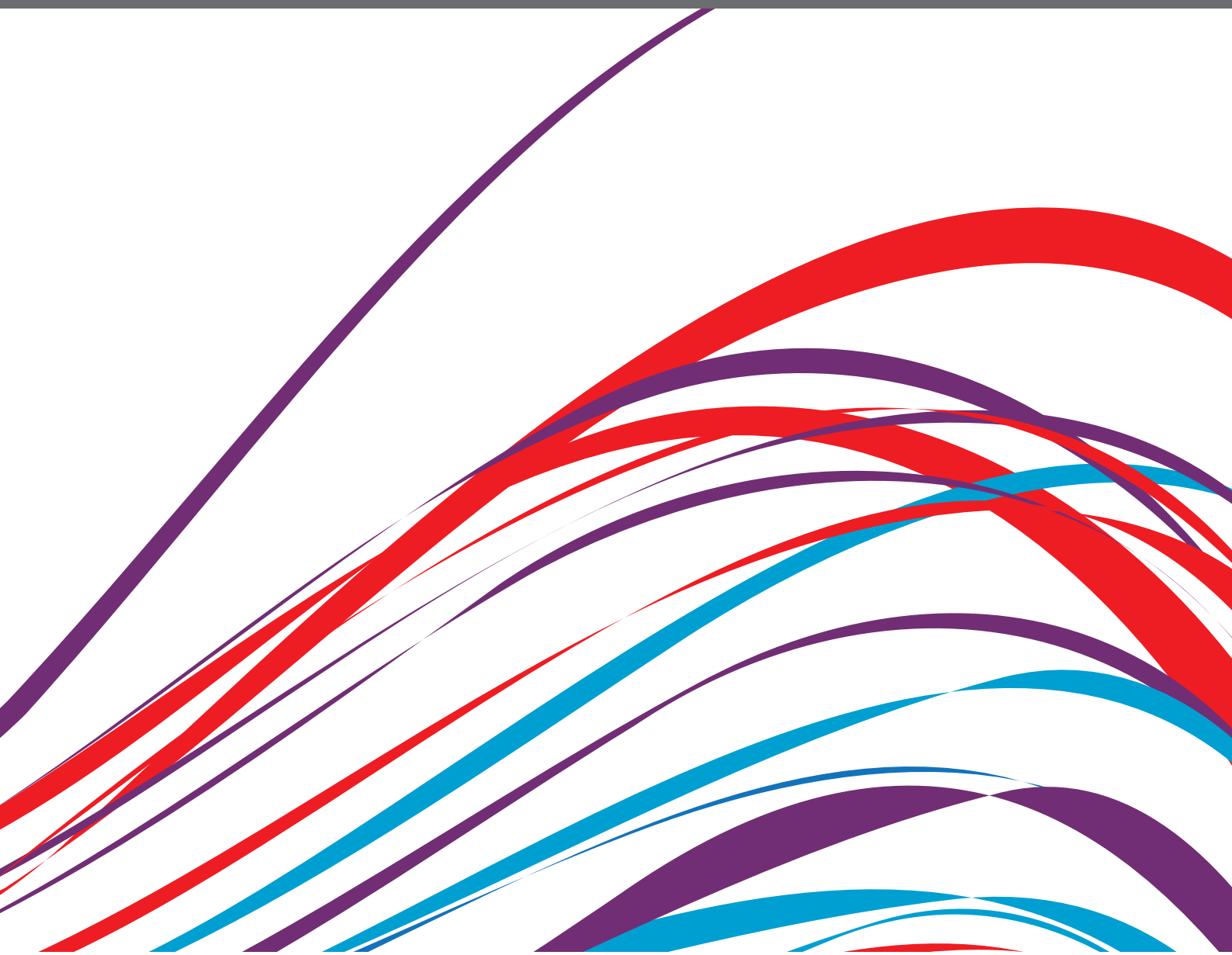

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PERCUTANEOUS MITRAL VALVE INTERVENTIONS (REPAIR): CURRENT INDICATIONS AND FUTURE PERSPECTIVES

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EDITORIAL
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Editorial: Percutaneous Mitral Valve Interventions (Repair): Current Indications and Future Perspectives

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Keywords: mitral regurgitation, trans-catheter mitral valve repair, heart failure, structural heart intervention, mitral

Editorial on the Research Topic

Percutaneous Mitral Valve Interventions (Repair): Current Indications and Future Perspectives

Mitral regurgitation (MR) is one of the most common valvular heart diseases in both European and U.S. populations, with its prevalence increasing with age (1). Severe MR strongly and negatively impacts prognosis, causing chronic left ventricle (LV) volume overload that culminates over time in the irreversible dilation and dysfunction of cardiac chambers. For this reason, delivering a timely treatment for symptomatic patients with moderate-to-severe MR represents a therapeutic priority.

To date, no single treatment option for MR could be considered the gold-standard, since disease- and patient-related characteristics can differ widely. Historically, surgery [mitral valve (MV) replacement or repair] has been the therapeutic cornerstone for MR, and is still considered the first-line therapy for patients with MR. However, in recent years, progressive technological improvements in the field of interventional cardiology have allowed us to approach MR with different trans-catheter techniques (mainly targeting the MV leaflets), which offer the benefits of being less invasive and having shorter patient recovery times. These advantages translate in a therapeutic alternative to conventional surgery for high-risk surgical or inoperable MR patients.

The knowledge that the MV is a complex anatomical apparatus has shed light on the etiology of functional MR (FMR), a disease primarily of the LV and/or atrium. Due to the lack of strong evidence concerning surgical benefit (2, 3), treatment of FMR still represents an unmet clinical need. In this setting, percutaneous interventions are considered a valid therapy in symptomatic patients. Different types of transcatheter treatments have been developed. Most of the available evidence is derived from MitraClip (Abbott Vascular, Abbott Park, Illinois, USA), the most used and studied percutaneous edge-to-edge repair system. In fact, the *Endovascular Valve Edge-to-Edge REpair Study* (EVEREST II) trial demonstrated MitraClip safety and efficacy in a cohort of MR patients [∼75% degenerative (DMR) and ∼25% FMR] when compared to conventional surgery (4). Hence, MitraClip is often considered the first transcatheter therapeutic option in both DMR and FMR for patients deemed unsuitable for cardiac surgery. However, recent randomized controlled trials (RCTs) focusing only on FMR provided conflicting results concerning MitraClip efficacy over medical therapy at 2 years: the *COAPT* trial (5) showed clear mortality and heart failure hospitalization rate reductions in patients treated with MitraClip, whereas the *MITRA-FR* trial (6) did not. Many explanations have been postulated for these diverging results, with the most reliable represented by the different stages of FMR patients studied: *MITRA-FR* enrolled patients with more remodeled and dysfunctional LV as well as less severe MR as compared to the *COAPT* population. This aspect underlies the pivotal need to treat FMR before patients enter an advanced "too-late" disease stage. New insight will be derived from the *RESHAPE-HF2* RCT (NCT02444338):

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420 patients suffering from symptomatic chronic heart failure with moderate-to-severe or severe FMR and reduced LV ejection fraction will be randomized to either optimal standard of care therapy or MitraClip device plus optimal standard of care therapy. The primary endpoint will consist of a composite rate of recurrent heart failure hospitalizations and cardiovascular death at 24 months. MitraClip is also not the only transcatheter option available. During the last few years, several transcatheter devices have been developed, mimicking different surgical techniques, and many others have started pre-clinical assessment. Beyond MitraClip, indirect and direct MV annuloplasty and chordal replacement systems have been studied. However, to date all these other treatments should still be considered and reported as experimental therapies, because the data was derived from studies with smaller sample sizes and shorter follow-ups.

On the other hand, since the underlying MR mechanism represents a major therapeutic success determinant, a wider therapeutic portfolio will increase the rate of procedural success and durability, reflecting the possibility to select a tailored therapeutic strategy. Transcatheter edge-to-edge repair, indirect and direct MV annuloplasty, and chordal replacement can also be seen as complementary therapeutic options, able to maximize the procedural success. However, large data concerning a combined use are still missing. Undoubtedly, the future of MR treatment will also include transcatheter MV replacement (TMVR). Despite this prediction, transcatheter repair therapies will remain an important part of the therapeutic armamentarium for MR, given their ability to preserve the complex inner MV anatomy. However, transcatheter repair therapies such as MitraClip may close the door to further interventions: once implanted, TMVR will be not feasible anymore. For this reason, the ongoing challenge is to choose the *right* device for the *mechanism* of MR, affecting the *given* patient. To achieve an optimal therapeutic goal, a multidisciplinary assessment of every patient is essential. The referring cardiologist, anesthesiologist, cardiovascular imaging specialist, cardiac surgeon, and interventional cardiologist should all confer on the decision together.

This journal is entirely dedicated to the current indications and future perspectives of percutaneous MV interventions. A comprehensive understanding of MV anatomy, physiology, and pathophysiology (Topilsky) is critical to achieve a successful MR reduction. For this purpose, patient and device selection utilizing a multi-modality cardiac imaging assessment is essential, since well-established feasibility criteria have been provided for several transcatheter devices. Imaging role will be also pivotal in the near future, considering advancements in TMVR (specifically to address its pre-procedural feasibly and prevent left ventricle outflow obstruction) (7). Moreover, although transesophageal echocardiography is now the intra-procedural guide in all interventions (Khalique and Hahn), in the near future intracardiac echocardiography (ICE) will be a concrete potential alternative to transesophageal echocardiography, mitigating the need for endotracheal intubation (8). Detailed overviews of current and future transcatheter systems are provided, ranging from edge-to-edge clips repair (Khan et al.; Shah and Jorde), direct (Gasior et al.), and indirect (Patterson et al.) MV annuloplasty, and chordal repair (Fiocco et al.). Lastly, emerging devices have been analyzed, reporting on available clinical as well as pre-clinical experience (Mangieri et al.) and potential procedural complications (Gheorghe et al.). In conclusion, transcatheter MV repair devices are validated therapeutic options able to accommodate a larger variety of MV anatomies, despite the fact that long-term durability results are still required.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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MINI REVIEW
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Indirect Annuloplasty to Treat Functional Mitral Regurgitation: Current Results and Future Perspectives

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The incidence of mitral regurgitation (MR) is approximately 1.7% in the developed world, and this increases to more than 10% in patients aged over 75 years. Functional (or secondary) mitral regurgitation (FMR) is defined as poor leaflet coaptation and tethering secondary to either ischemic or non-ischemic left ventricular (LV) dysfunction and dilatation. FMR is more common than degenerative (or primary) MR and is associated with significantly worse outcomes in patients with heart failure, post myocardial infarction and following coronary artery bypass graft surgery. Patients with severe degenerative MR have excellent outcomes with surgical repair, however the benefits of surgery in FMR are less clear. Although annuloplasty is associated with a lower operative mortality compared to replacement, the recurrence rate of mitral regurgitation is high in patients with FMR and neither surgical repair or replacement have been shown to reduce hospitalisation or death in FMR. Furthermore, nearly half of patients are deemed too high risk for surgery and therefore most patients are managed conservatively and there remains an unmet clinical need. Transcatheter mitral valve interventions are an emerging alternative for those at high surgical risk. This mini review focuses on indirect mitral annuloplasty: anatomical considerations, patient selection, current devices, implantation techniques and the associated clinical outcome data.

Keywords: mitral regurgitation, annuloplasty, transcatheter, functional mitral regurgitation, indirect annuloplasty

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BACKGROUND

The incidence of mitral regurgitation (MR) is ∼1.7% in the developed world, and this increases to more than 10% in patients aged over 75 years (1). Functional (or secondary) mitral regurgitation (FMR) is defined as poor leaflet coaptation and tethering secondary to either ischemic or non-ischemic left ventricular (LV) dysfunction and dilatation. FMR is more common than degenerative (or primary) MR and is associated with significantly worse outcomes in patients with heart failure, post myocardial infarction and following coronary artery bypass graft surgery (2–4). Patients with severe degenerative MR have excellent outcomes with surgical repair, however the benefits of surgery in FMR are less clear (5, 6).

Current guidelines for the management of severe FMR recommend consideration of surgical intervention (repair or replacement) in symptomatic patients only following optimization of medical treatment ± cardiac resynchronization therapy (7, 8). Although annuloplasty is associated with a lower operative mortality compared to replacement, the recurrence rate of mitral regurgitation is high in patients with FMR and neither surgical repair or replacement have been shown to reduce hospitalization or death in FMR (5, 6, 9). Furthermore, nearly half of patients are deemed too high risk for surgery and therefore most patients are managed conservatively and there remains an unmet clinical need (10).Transcatheter mitral valve interventions are an emerging alternative for those at high surgical risk. These treatments are rapidly evolving with a number of novel transcatheter mitral techniques now available, many of which mimic surgical repair. Due to the complexity of the mitral valve apparatus, various techniques have been designed to target certain aspects of failure of the mitral apparatus. As FMR is predominantly a disease of the LV with failure of leaflet coaptation, the aim is to reduce the septal-lateral distance of the mitral annular plane and/or increase coaptation of the leaflets. Transcatheter annuloplasty techniques serve to reduce annular dimensions and differ from surgical techniques in that they provide the option of both direct and indirect approaches (11–15), each of which have their own potential advantages. Direct annuloplasty enables closer approximation to the mitral valve, whereas indirect annuloplasty is potentially a much simpler procedure. This mini review focuses on indirect mitral annuloplasty: anatomical considerations, patient selection, current devices, implantation techniques, and the associated clinical outcome data.

ANATOMICAL CONSIDERATIONS FOR INDIRECT ANNULOPLASTY

The coronary sinus (CS) drains the majority of blood from the heart. It arises from the termination of the great cardiac vein, running through the left atrioventricular groove, emptying into the right atrium. The CS lies in close anatomical proximity to the mitral annulus (**Figure 1A**) (16). Indirect annuloplasty therefore utilizes the CS to exert a constraining force on the mitral annulus, thereby decreasing its septal-lateral diameter, improving leaflet coaptation and reducing the degree of mitral regurgitation. However, anatomical variation between individuals may limit the clinical efficacy of this approach. Indirect annuloplasty relies on the proximity of the CS to the mitral annulus—however, the CS is located superior to the mitral annulus in a significant number of patients and is often higher posteriorly than anteriorly (17). Furthermore, the distance between the mitral annulus and CS tends to increase in patients with dilated ventricles and severe MR (18). This could therefore explain the variation in clinical efficacy amongst different indirect annuloplasty devices.

Importantly, the circumflex coronary artery lies within close proximity of both the CS and mitral annulus. Studies have demonstrated that the vessel exhibits a deep course between the CS and mitral annulus in up to two thirds of patients (19, 20). There is therefore a theoretical risk of compression and myocardial infarction associated with indirect annuloplasty. Accurate pre-procedural imaging assessment of the venous system, coronary sinus anatomy, and mitral annular plane is essential to determine suitability and ensure appropriate patient selection prior to device implantation.

PATIENT SELECTION FOR ANNULOPLASTY TECHNIQUES

The complexity of the mitral valve apparatus necessitates patient-specific tailoring using the appropriate reparative technique because no single transcatheter technology "fits-all." Assessment of suitability prior to annuloplasty is crucial and decision with regard to repair technique should be based on clinical and anatomical characteristics. When selecting the appropriate transcatheter therapy, it is important to first establish the primary mechanism of MR, it's severity and the imaging criteria that will predict procedural success. Traditionally, annuloplasty, either with direct or indirect percutaneous techniques are favored where annular dilatation is the predominant pathology. Surgical features of annuloplasty failure should also be taken into consideration, these include but are not limited to, increased annular dimensions ($\geq$3.7 cm), increased systolic tenting height, complex jet(s) of mitral regurgitation and lateral wall motion abnormalities (21, 22). Furthermore anatomical considerations including the position of the CS in relation to the mitral annulus and position of the coronary arteries must also be taken into consideration. In **Table 1** we summarize the clinical and echocardiographic criteria for the currently available indirect annuloplasty techniques and the comparable reduction in MR from the respective clinical trials and compare these to direct annuloplasty and edge-to-edge repair. Edge-to-edge repair may be the preferred initial therapy in FMR if the predominant mechanism of failure of coaptation is leaflet tethering or prolapse, as can be the case with ischemic MR, where leaflet tethering and annular dilatation can coexist. Percutaneous edge-to-edge repair joins the anterior and posterior leaflets using a clip, mimicking the surgical Alfieri technique and can be used in the treatment of both degenerative and FMR (25–27). Edge-to-edge repair has been shown to improve clinical outcomes in FMR with a greater benefit shown with increasing MR severity (23). Recent randomized trial data in favor of edge-to-edge repair in FMR would suggest a greater benefit in patients with severe heart failure symptoms (NYHA III-IV), larger regurgitant volume, with smaller LV end-diastolic dimensions (23, 28). However, assessment of patient suitability for edge-to-edge repair is necessary (**Table 1**) and increased severity of MR may necessitate more than one clip. The surgical Alfieri technique is often performed in conjunction with annuloplasty, as such there may be scope for performing combined transcatheter mitral interventions in these patients (see **Figure 1B**). Although this is yet to be demonstrated on a larger scale, reports of indirect or direct annuloplasty following edge-to-edge repair demonstrate reasonable outcomes. However, there is theoretical risk of mitral

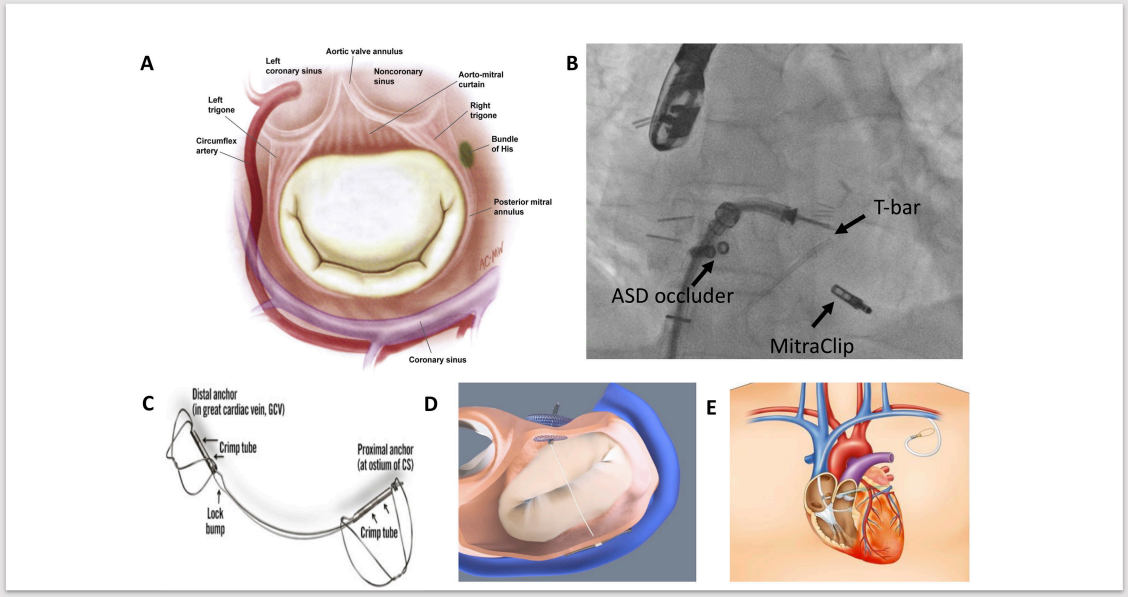

FIGURE 1 | (A) Anatomical relationships of the mitral valve, demonstrating the close proximity of the mitral annulus, coronary sinus, circumflex artery and conduction system. Adapted and reprinted from Carpentier's Reconstructive Valve Surgery *with permission from Elsevier.* **(B)** Fluoroscopic image of MitraClip implantation as a second procedure, following a previous ARTO device; fluoroscopic landmarks for this are the Atrial Septal Defect (ASD) occluder device and the T-Bar. **(C)** The Carillon coronary sinus implant (Cardiac Dimensions) device. *Adapted and reprinted from Eurointervention, Natarajan et al, The big parade: emerging percutaneous mitral and tricuspid valve devices, 2017, with permission from Europa Digital & Publishing.* **(D)** Graphical image of the ARTO (MVRx Inc) device following deployment, with two anchors either side of the tether. In this image projection, the T-bar anchor sits inferiorly and the atrial septal anchor (occluder device) sits superiorly. *Adapted and reprinted from Eurointervention, Natarajan et al, The big parade: emerging percutaneous mitral and tricuspid valve devices, 2017, with permission from Europa Digital & Publishing.* **(E)** Graphical image demonstrating the anatomical course of cerclage annuloplasty to reduce mitral annular dimensions. Adapted and reprinted from Mitral Loop Cerclage Annuloplasty for Secondary Mitral Regurgitation, Park et al *with permission from Elsevier*.

valve outflow obstruction with more than one device, thus more data are required if there is to be a role for this in the future.

CARILLON DEVICE

The Carillon coronary sinus implant (Cardiac Dimensions) is currently the only CE approved indirect annuloplasty device undergoing clinical use. The main advantage is its simplicity and safety profile, and more than 700 procedures have been performed worldwide to date (29). The Carillon device is a fixed length nitinol system that is delivered to the CS via a 9 French delivery system through the right external jugular vein (**Figure 1C**) (30). The device is comprised of a distal and proximal anchor. The distal anchor is deployed deep in the CS encircling the mitral annulus and traction is applied thereafter through foreshortening of the central nitinol element, thus constricting the coronary sinus by cinching the posterior peri-annular tissue and reducing mitral annular dimensions. Following confirmation of reduced mitral annular dimensions, a check angiogram is performed to ensure circumflex patency prior to final device release.

Two clinical trials of safety and feasibility have been conducted to date. The Carillon Mitral Annuloplasty Device European Union Study (AMADEUS) study successfully implanted devices in two thirds of patients selected to undergo the procedure. Patients in the AMADEUS study had only modest reductions in MR at 6-month follow up (14). The Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial, 36 patients underwent device implantation and 17 had the device recaptured, the latter were used as a comparator group. There was no difference in the composite safety endpoint and the reduction in MR was more significant in the cohort that received the device, with an average decrease in regurgitant volume of 17 ml. This was accompanied by a significant reduction in LV systolic and diastolic dimensions at 12 and 24 months following successful implantation (31).

More recently, the outcomes of the REDUCE-FMR trial of efficacy and safety of Carillon implantation vs. sham control in patients with functional MR secondary to dilated ischemic or non-ischemic cardiomyopathy have been presented (24). The primary efficacy outcome of reduction in mitral regurgitant volume at 1 year was met (−7.1 vs. 3.3 ml; $P = 0.03$), the numerical reduction of MR was even more notable in the per protocol analysis (−12.5 vs. 1.3 ml; $p = 0.06$). Furthermore, no significant difference in major adverse cardiovascular and cerebrovascular events was demonstrated between the Carillon and sham control cohort. The CARILLON FDA trial (NCT03142152) of 450 patients randomized to the CARILLON device with optimal heart failure therapy vs. optimal heart failure therapy alone is currently open to recruitment in the United States.

TABLE 1 | Summary of the indirect annuloplasty devices in use for functional mitral regurgitation, criteria for implant and supporting data compared with direct annuloplasty device and MitraClip.

Technique	Device	Indication	Trial & design	Number of patients	Imaging & clinical inclusion criteria	Mean reduction in RV (mL)	CE mark
Indirect annuloplasty	Carillon	Secondary/FMR with annular dilatation	AMADEUS phase I safety trial	48 (30 received device)	Moderate or severe FMR, EF<40%, NYHA class II-IV symptoms	−8.8 (6 months), $P < 0.001$	YES
			TITAN prospective non-randomized multicentre trial	53 (36 received the device)	Moderate or severe FMR, EF<40%, NYHA class II-IV symptoms despite OHFT, 6-min walk 150–450 m	-17 ± 12 (1 year), $P < 0.001$	
			REDUCE FMR sham control trial	87 device groups vs. 33 sham procedure	Moderate or severe FMR, EF<50%, NYHA class III-IV symptoms despite OHFT, LVEDD >55 mm	−7.1 vs. + 3.3 controls (1 year), $p = 0.03$	
	ARTO	Secondary/FMR with annular dilatation	MAVERIC phase 1 safety trial	11	Moderate or severe FMR, EF < 40%, LVEDD > 50 mm & ≤75 mm	−25.9 (30-days), *p* NS	NO
	Mitral Loop Cerclage System	Secondary/FMR with annular dilatation	Phase 1 trial	5	Severe FMR (RV ≥ 30 mL, RF ≥ 50 mL, EROA ≥ 0.20 cm^2), NYHA class III-IV despite OHFT	−36.3 (6 months), *p* NS	NO
Direct annuloplasty	Cardioband (Edwards Lifesciences, California, USA)	Secondary/FMR with annular dilatation	Single-arm, multicenter prospective trial	31	Severe FMR despite OHFT including CRT	−11.4 (6 months), $p = 0.063$	YES
Edge to edge repair	MitraClip (Abbott Vascular, Illinois, USA)	Primary degenerative (FDA approved) and ischemic MR (secondary) with annular dilatation	COAPT Randomized controlled open label trial	302 device vs. 312 control (OHFT)	Moderate to severe FMR despite OHFT, EF 20–50%, LVEDD ≤70 mm NB: more than one clip or alternative to be considered if flail width>15 mm, gap>10 mm, coaptation depth >11 mm; not suitable for rheumatic or bileaflet flail	NS, however ≤moderate MR in 94.8 vs. 46.9% controls, $P < 0.001$	YES

Nickenig et al.(11), Stone et al.(23), Goldberg et al. (24) CRT, cardiac resynchronization therapy; EF, ejection fraction; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; LVEDD, left ventricular end diastolic diameter; NS, not specified; NYHA, New York heart association; OHFT, optimal heart failure therapy; RF, regurgitant fraction; RV, regurgitant volume.

ARTO DEVICE

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 1D**). Erglis et al. (15) Implantation is performed using transesophageal echocardiographic guidance with the patient under general anesthetic. Two venous access sites are required to deliver the device. One of two magnetic catheters is positioned in the coronary sinus over the lateral wall of the left atrium through right jugular venous access. The second magnetic catheter is positioned across the atrial septum via femoral venous access and trans-septal puncture. These two catheters are then manipulated and linked magnetically in the posterior left atrium adjacent to the posterior mitral annulus. A small puncturing wire is then used to create a connection between the two magnetic catheters. Routine catheter exchanges are performed to deliver a coronary sinus anchor (T-bar) and atrial septal anchor, connected by a suture whose length can be adjusted to reduce the anteroposterior (AP) diameter of the mitral annulus until an acceptable reduction in MR is achieved. This suture is then locked and cut.

In the first phase of the MitrAl ValvE RepaIr Clinical (MAVERIC) trial, 11 patients underwent successful device implantation with one device displacement and one pericardial effusion requiring surgical intervention. At 30-day follow up, a decrease in regurgitant volumes from 45.4 ± 15.0 ml to 19.5±10.2 ml was demonstrated with a beneficial effect on LV volumes. LV end-systolic volume index improved from 77.5 ± 24.3 ml/m^2 to 68.5 ± 21.4 ml/m^2, and LV end-diastolic volume index from 118.7 ± 28.6 ml/m^2 to 103.9 ± 21.2 ml/m^2. Mitral annular AP diameter decreased from 45.0 ± 3.3 mm to 38.7 ± 3.0 mm with an associated improvement in New York Heart Association (NYHA) functional class (32). Data at 2-year follow up demonstrated a consistent significant improvement in functional MR grade, regurgitant volumes (39.1 ± 11.6 ml vs. 14.0 ± 10.3 ml; $p < 0.001$) and reduction in mitral annular AP diameter (45.9 ± 3.1 mm vs. 39.8 ± 3.3 mm; $p < 0.001$). These changes were associated with an improvement in symptomatic status from 81.8% NHYA functional class III/IV at baseline to 60.0% NYHA functional class I/II at 2 years (33). Phase II of the MAVERIC trial is ongoing with 34 patients enrolled at 8 sites.

MITRA LOOP CERCLAGE SYSTEM

The Mitral Loop Cerclage annuloplasty system (Tau-PNU Medical Co, Ltd.) consists of a stainless-steel tension element delivered using a multistep procedure to form a continuous loop from the coronary sinus to a basal septal perforator coronary vein and right ventricular outflow tract (**Figure 1E**) (13). It has a coronary sinus tricuspid bridge device (that straddles and protects the septal tricuspid leaflet and coronary conduction system) completing the loop. There is an arch-like coronary artery protection element to prevent compression of the circumflex and the device can be tensioned in real-time under echocardiographic guidance to titrate the indirect annuloplasty.

Implantation is performed under moderate sedation (transthoracic echocardiogram) or general anesthesia (transesophageal echocardiogram). Access is via 19 Fr sheaths in the left subclavian and right femoral vein. A dual lumen coronary sinus guiding catheter is introduced into the coronary sinus via the left subclavian and contrast injection used to identify a basal septal perforator vein through which a stiff tipped peripheral guidewire is introduced and used to traverse the septum into the right ventricular outflow tract before snaring into the femoral vein. The tension element is then connected to the guidewire using heat-shrink tubing and pulled into position through the CS into the interventricular septum before loop snaring of the distal guide wire tip from the femoral vein into the subclavian. Next, the bifid coronary sinus tricuspid valve bridge is advanced over the two free ends of the tension element and the coronary artery protection element positioned with diagnostic angiography. Tension is then applied to reduce the septal lateral distance and the tension device is locked and embedded in the subclavian pocket.

First in human results demonstrate successful implantation in 4 out of 5 patients. Failure to implant in one was due to unsuitable anatomy. Of those who underwent successful implantation, one patient suffered myocardial infarction and one patient died of refractory heart failure at 6 weeks. All patients demonstrated an immediate reduction in regurgitant volume. At 6-month follow up, regurgitant volume continued to decrease in the remaining 3 patients and was associated with a reduction in left atrial and LV systolic and diastolic size. Interestingly, two patients reverted to sinus rhythm at the end of the procedure (34). This was speculated to be secondary to electrical remodeling induced by the cerclage device, but may also be as a result of reduced cardiac dimensions.

FAILED INDIRECT ANNULOPLASTY DEVICES

Coronary sinus constriction can lead to complex torsional deformation due to the complexity of the mitral annular plane and position of the CS in relation to the mitral annulus. This has unfortunately led to the failure of two previously developed devices despite encouraging early clinical safety and feasibility data (35, 36). The Viacor Percutaneous Transvenous Mitral Annuloplasty (PTMA) device comprised nitinol rods positioned in the CS to compress the posterior mitral annulus—however, device fracture in one patient led to a late, fatal coronary sinus laceration and removal from clinical use. The MONARC device (Edwards LifeSciences) was a spring-like band deployed in the coronary sinus with two self-expanding stents at either end (36). However, this device is also no longer in use due to a number of reported fractures between the band and the stents.

FUTURE DIRECTIONS AND LIMITATIONS

Functional MR is an unmet clinical need in those on maximal medical therapy but considered too high risk for conventional

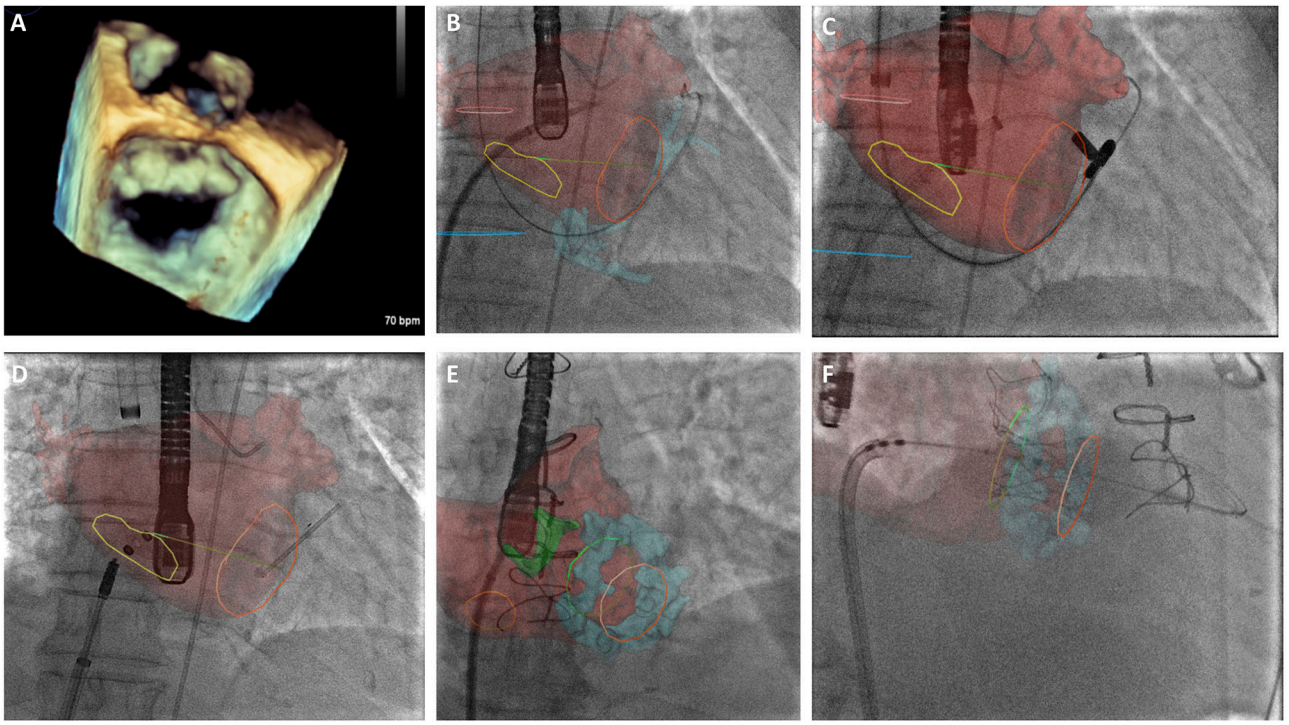

FIGURE 2 | (A) 3-Dimensional transesophageal echocardiographic (TEE) real-time reconstruction of the mitral valve annulus and leaflets as a preliminary investigation to determine anatomical suitability for transcatheter mitral intervention. **(B)** CT overlay with real-time image fusion to demonstrate the optimal site for trans-septal puncture for ARTO case. Yellow line delineates inter-atrial septum, left atrium is superimposed in red. **(C)** CT overlay with real-time image fusion during magnet positioning during ARTO case **(D)** real-time image fusion demonstrating T-bar and atrial septal defect (ASD) occluder device device positioning relative to mitral annulus (orange circle) and inter-atrial septal markers (yellow circle), respectively. **(E)** CT overlay with real-time image fusion during transeptal puncture for transcatheter mitral valve implantation in mitral annular calcification identifying interatrial septum (orange circle), atrial anatomy (red) and mitral annular calcification (blue), aortic bioprothesis is also delineated (green). **(F)** CT overlay with real-time image fusion to facilitate transcatheter mitral valve in MAC positioning, atrial anatomy (red) and mitral annular calcification (blue) are visualized in addition to the superior (green) and inferior markers (orange).

surgery. Annuloplasty techniques and the associated data are promising. However, annuloplasty techniques may not be suitable for all patients. Anatomical variation between individuals may limit the clinical efficacy of this approach as indirect annuloplasty relies on the proximity of the CS to the mitral annulus. Increasing LV dilatation further increases the distance between the mitral annulus and CS potentially rendering this approach ineffective. The reduction in annular dimensions from percutaneous interventions have not been as large as suggested in the surgical literature and longer-term clinical data are required to ensure safety and efficacy of these devices due to the risk of device erosion and coronary occlusion and also to assess for recurrence of MR.

The recent results of the MITRA-FR and COAPT trial have helped define a patient population in whom there is potential benefit from MitraClip implantation (**Table 1**). The surgical Alfieri technique is frequently performed in conjunction with annuloplasty, and there may be scope for performing combined transcatheter mitral repair in these patients, however this is yet to be demonstrated on a larger scale. It would be advisable for centers providing transcatheter mitral interventions to be trained in a number of techniques so as to appropriately select the patient cohort that would benefit from a specific technique. An increased appreciation of the mitral valve apparatus will no doubt aid development of further novel mitral technologies and second and third generation devices are anticipated to improve procedural safety and success rates. Such devices will require large scale clinical validation and Heart Team involvement will be essential to determine patient suitability. Due to the complexity of the mitral valve apparatus, Heart Team decision making will require evaluation of patient-specific anatomical characteristics using novel imaging techniques, including 3D TEE and CT image fusion (**Figures 2A–F**). This will aid decision-making and guide periprocedural planning and implantation to ensure successful procedures with minimal complications.

CONCLUSIONS

An increase in anteroposterior (AP) mitral annular diameter is the common final pathway in the development of functional MR and associated with worsening clinical outcomes in heart failure and post myocardial infarction. Shortening of the AP dimension is therefore critical to alleviating MR. The aim of transcatheter mitral repair is to balance the increase in peri-procedural safety (reduced risk) with a sufficient reduction in MR for it to be effective. Annuloplasty, both direct and indirect,

leaflet repair and chordal repair are all viable options based upon well-established surgical techniques and a combination of these approaches may provide the most effective resolution of MR. Current predictors of MR recurrence following surgical repair include baseline LV end-diastolic diameter >65 mm, posterior mitral leaflet angle >45 degrees and mitral coaptation depth >10 mm (37). However, the relevance of these for the success of percutaneous interventions remains unknown. Furthermore, there are numerous challenges to effective treatment of MR, including anatomical variation and the complexity of the mitral valve apparatus, imaging constraints and currently available technologies. There remain important considerations when determining suitability for percutaneous mitral valve interventions, including appropriate patient selection (moderate vs. severe MR, normal vs. impaired LV function) and choice of device based on anatomical characteristics. Although further work is required to ensure safety and durability of these devices, increased understanding of the true incidence, natural history and pathophysiology of MR, will enable better targeted device therapy in this cohort.

AUTHOR CONTRIBUTIONS

SR manuscript conception, design, and critical revision. BP manuscript critical revision. RR manuscript critical review and revision. TP manuscript conception, design and critical revision. HA critical revision of the manuscript. CA critical revision of the manuscript.

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REVIEW
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Percutaneous Mitral Valve Interventions (Repair): Current Indications and Future Perspectives

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Mitral valve regurgitation (MR) is the commonest valvular abnormality encountered among adult patients with cardiac valvular disease and conveys significant morbidity and mortality. The mitral valve is a complex anatomical structure and etiology for regurgitation is classified as either *primary* or *secondary* MR. Identification of the etiology in severe MR is critical in determining the appropriate treatment strategy. Transcatheter mitral valve repair (TMVR) is a minimally invasive technique for treatment of selected patients with symptomatic chronic moderate-severe or severe (3 to 4+) MR. While surgery remains the mainstay for treatment in *primary* MR, several technological advances within the last decade have made transcatheter mitral valve intervention increasingly feasible and safe in clinical practice. Use of TMVR in patients with severe MR has successfully reduced patient symptoms, disease morbidity, improved quality of life, and facilitated reverse remodeling with potential for a survival advantage among certain patients with *secondary* MR. Recent randomized controlled trials on MitraClip use in *secondary* MR have reinvigorated interest in this disease and refocused our attention on optimizing patient selection and timing of intervention to maximize benefit from using such percutaneous devices. In our review, we discuss etiologies and pathophysiology in both acute MR and development of chronic severe MR. We discuss management strategies for MR among patients based on etiology, particularly percutaneous mitral valve interventional therapies. We perform an extensive review comparing and contrasting existing data on safety, efficacy, durability, and appropriate patient selection related to MitraClip implantation in both *primary* and *secondary* MR. Lastly, we explore percutaneous MV therapies beyond the MitraClip as we await larger scale trials on these devices prior to them making way into day-to-day practice.

Keywords: mitral regurgitation, functional mitral regurgitation, percutaneous mitral repair, MitraClip device, degenerative mitral regurgitation (DMR), heart failure, medical management, mitral surgery

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STRUCTURE AND ANATOMY OF THE MITRAL VALVE

The mitral valve (MV) is complex and involves synchronous participation of several anatomical structures including valvular leaflets, chordae tendinae, papillary muscles, mitral annulus, and left ventricular (LV) myocardium to facilitate unidirectional passage of blood from left atrium into the ventricle during diastole, and preventing regurgitation during systole (1) (**Figure 1**). Anatomical changes at any level can potentiate valvular dysfunction particularly abnormal leaflet closure and regurgitation of blood. The MV comprises of anterior (aortic) and posterior (mural) leaflets, with three segments each (A1A2A3, P1P2P3) labeled from the lateral to medial aspect of heart (**Figure 2**). The posterior leaflet

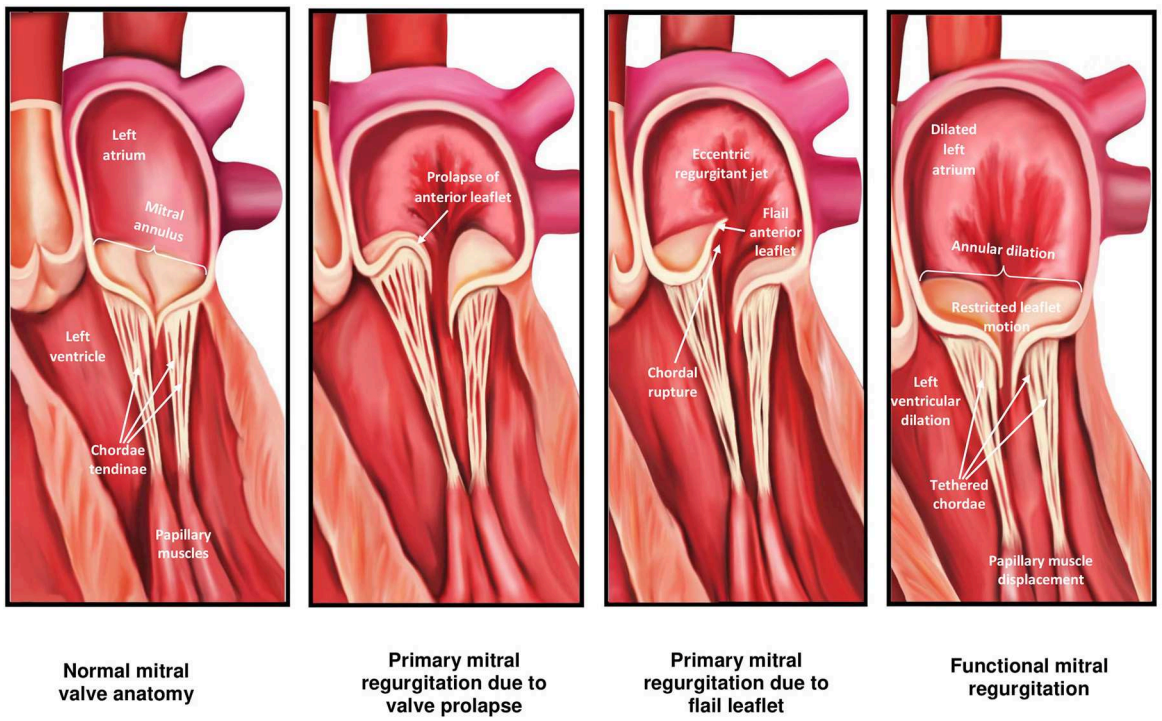

FIGURE 1 | Mitral valve apparatus and etiologies for mitral regurgitation.

has more prominent notching along its free edge, clearly dividing the leaflet into three scallops or segments. The mitral annulus is a saddle shaped structure composed of fibrocollagenous tissue attached to the mitral leaflets. The anterior portion of the mitral annulus is attached to the fibrous trigones which contain conduction tissue whereas the posterior annulus is less well-developed, more muscular and prone to dilation. Mitral valvular regurgitation is the commonest valvular disorder among adults (2, 3). Failure of complete coaptation and adequate symmetrical apposition of both mitral leaflets results in varying degree of MR. Identifying the etiology for failure of underlying MV function can aid in developing an appropriate treatment strategy.

ETIOLOGY OF MR

When it comes to understanding the etiology of MR, designating the MR as either "*primary* or *degenerative*" (related to anatomical abnormalities in valve leaflets and/or chordae tendinae) vs. "*secondary* or *functional*" (usually related to systolic tethering of anatomically intact MV leaflets due to annular dilation in the setting global or regional LV wall motion abnormalities) is commonly the initial step [**Table 1**; **Figures 1**, **2**; (3)]. In *functional* MR, the LV becomes more spherical and this is associated with retraction of the papillary muscles and chordae tendinae along with widening separation of the valvular leaflets. In most cases, MR worsens over time and has a relatively chronic picture. Less commonly presentation can be acute when severe MR results from either rupture of chordae tendinae or papillary muscle and infective endocarditis. In the developed world, the commonest etiology for MR is likely *degenerative* MV disease as a result of the high prevalence of MV prolapse (MVP) in the general population from myxomatous degeneration and chordal stretching (4). However, in one single-center study evaluating 1,095 patients with significant MR and heart failure (HF) symptoms, *functional* MR (∼75%) was more common followed by *degenerative* MR (5). An additional etiology for mitral regurgitation has been noted among patients with isolated atrial fibrillation in the presence of normal mitral leaflet, subvalvular and LV anatomy called "*atrial functional*" MR. It has been attributed to left atrial enlargement and dilation in mitral annulus as the primary mechanism for mitral leaflet malcoaptation (6). Such a new classification for MR solely secondary to dilation of the mitral annulus has been debated and the prevalence of *atrial functional* MR in prior MR studies is somewhat unknown due to its poor recognition as a separate entity (7). While both classes of atrial and ventricular *functional* MR have been associated with normal leaflet anatomy, accumulating data seems to suggest that alterations in the extracellular matrix within the mitral leaflets and insufficient leaflet remodeling relative to the increase in mitral annulus also contribute to worsening of MR (8–10).

PATHOPHYSIOLOGY OF ACUTE AND CHRONIC MR

Acute MR

Acute MR results in acute left atrial and LV volume overload, increasing ventricular preload and stroke volume as consequence of the Frank-Starling mechanism. In addition, there is a

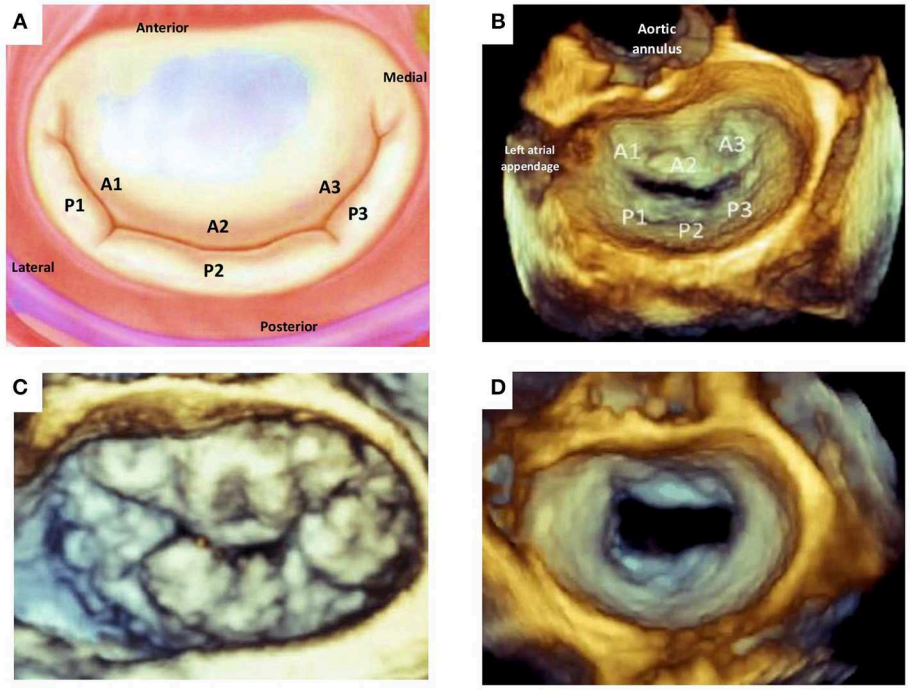

FIGURE 2 | Mitral valve leaflet anatomy. **(A)** Schematic of normal mitral valve. **(B)** Corresponding 3D TEE view of the atrial aspect of normal mitral valvular anatomy. **(C)** 3D TEE image of a patients with multi-leaflet prolapse (Barlow's disease). **(D)** 3D TEE image of incomplete central closure of mitral valve during systole and resultant severe functional mitral regurgitation. TEE, transesophageal echocardiography.

reduction in LV systolic wall stress and afterload with increase in LV ejection fraction (EF). The acute increase in volume from MR into a non-compliant left atrium results in marked elevation in left atrial and pulmonary venous pressures, causing pulmonary edema.

Chronic MR

As patients evolve from acute to chronic MR, the LV dilates and changes from a small hyperkinetic chamber in acute MR to a large compliant chamber (11). During this transition, rearrangement of myocardial fibers and addition of sarcomeres results in eccentric LV hypertrophy (12). In the early compensated phase of chronic MR, the LV is able to maintain normal wall stress, high stroke volume and adequate cardiac output at the expense of increased LV end diastolic volume (LVEDV). These temporal changes in LV structure result in normalized preload and afterload at the sarcomere level and thus compensated chronic MR. During this phase, the left atrium enlarges in size with improvement in atrial compliance and decline in pulmonary venous pressures. As the underlying disease progresses, however, usually over years the LV dilates further, afterload increases and LV contractility eventually worsens with decompensation of disease status (13). The underlying pathophysiology for *atrial functional* MR is less well-studied, and likely related to left atrial enlargement, displacement of posterior annulus onto the crest of the LV, close apposition of posterior mitral leaflet to the LV wall, reduction in posterior leaflet area for coaptation, and counterclockwise torque of the anterior mitral annulus causing tethering of the anterior mitral leaflet with leaflet tenting (14). While patients are often asymptomatic during the compensated stage of disease, there is growing interest in timing intervention for MR early to prevent decompensation. Recent trials on percutaneous MV repair have rejuvenated interest on the interplay between LV dysfunction and degree of MR, to identify a phenotype more responsive to intervention.

DISEASE PROGNOSIS AND NATURAL HISTORY

Severe untreated MR has a fairly poor prognosis irrespective of etiology. In addition to reduced survival, several data point to worse quality of life and a time dependent increase in the burden of atrial fibrillation and HF symptoms with severe MR. Factors associated with worse outcomes among patients with severe MR can be seen in **Table 2** (15–19). Evolution of MR into the chronic compensated and decompensated stages occurs over many years to decades, depending on severity of the MR and cardiac structural changes. The 2014 American Heart Association/American College of Cardiology (AHA/ACC) Guideline for the Management of Patients With Valvular Heart Disease and 2017 focused update describe the nature of this transition to more advanced disease by defining stages for

TABLE 1 | Characteristics based on etiology of mitral regurgitation.

	Primary MR	Secondary MR
Prevalence	Higher mainly due to MV prolapse	Lower in general population
Mechanism	Pathology of ≥1 of the components of the valve (leaflets, chordae tendinae, papillary muscles, annulus)	Left ventricular dysfunction with papillary muscle displacement, LV dyssynchrony, associated leaflet tethering and annular dilation. Normal (or nearly normal) mitral leaflet and chordal structure
Associated diseases	• Myxomatous valve - Barlow's disease, Fibroelastic deficiency disease • Rheumatic valvular disease • Endocarditis • Radiation therapy, connective tissues disease, drug induced, mitral annular calcification, cleft mitral valve	• Dilated cardiomyopathy • Ischemic MR secondary to previous myocardial infarction • Hypertrophic cardiomyopathy
Carpentier functional classification type*	• Type I (leaflet perforation or cleft) • Type II (MV prolapse) • Type IIIa (rheumatic valve disease, drug induced MR, mitral annular calcification)	• Type I (atrial MR, non-ischemic cardiomyopathy) • Type IIIb (ischemic cardiomyopathy, LV dysfunction and systolic leaflet tethering)

**Type 1: normal leaflet motion. Type 2: excessive leaflet motion. Type 3a: leaflet restriction in systole and diastole. Type 3b: leaflet restriction in systole.*

TABLE 2 | Factors associated with worse outcomes with significant MR.

Factors associated with worse outcomes with significant MR
• Development of heart failure symptoms (Survival worse in NYHA functional class III/IV)
• New atrial fibrillation
• Right ventricular dysfunction*
• Severe tricuspid regurgitation*
• Functional etiology
• Echocardiographic parameters
- Effective regurgitant orifice area ≥40 mm^2 (primary MR)
- Effective regurgitant orifice area ≥20 mm^2 (secondary MR)
- LV ejection fraction <60% (LV systolic dysfunction)

**When studied with functional mitral regurgitation.*

clinical evaluation combining patient's functional status and hemodynamic data as seen in **Table 3** (3, 20).

The compensated phase of MR is considered benign without overt dilation of LV [LV end diastolic diameter (LVEDD) <60 mm, end systolic diameter (LVESD) <40 mm, end diastolic volume (LVEDV) <110 ml/m^2, end systolic volume <45 ml/m^2 and ejection fraction >60%], low arrhythmia burden and being relatively asymptomatic with mild to moderate exertion. The decompensated phase of disease is based upon presence of HF symptoms and suboptimal LV parameters secondary to

TABLE 3 | Stages of mitral regurgitation in chronic primary and secondary MR.

Grade	Definition	Valve hemodynamics	Symptoms
A	At risk for MR	• No jet or small central jet area < 20% LA • VC < 0.3 cm	None
B	Progressive MR	• Central jet MR 20–40% LA or late systolic eccentric jet MR • VC < 0.7 cm • Rvol < 60 ml • RF < 50% • ERO < 0.4 cm^2 • Angiographic grade 1 to 2+	None
C	Asymptomatic severe MR	• Central jet MR >40% LA or holosystolic eccentric jet MR • VC ≥0.7 cm • Rvol ≥60 ml • RF ≥50% • ERO ≥0.4 cm^2 • Angiographic grade 3 to 4+	None
D	Symptomatic severe MR	• Central jet MR >40% LA or holosystolic eccentric jet MR • VC ≥0.7 cm • Rvol ≥60 ml • RF ≥50% • ERO ≥0.4 cm^2 • Angiographic grade 3 to 4+	Decreased exercise tolerance Exertional dyspnea

MR, mitral regurgitation; VC, vena contracta; Rvol, regurgitant volume; RF, regurgitant fraction; ERO, effective orifice area; LA, left atrium.

failure of compensatory mechanisms (LVEDD >70 mm, LVESD >47 mm, LVEDV >160 ml/m^2, LVEDV >60 ml/m^2, LV ejection fraction <50%). The transition phase between these two disease phenotypes is less well-defined with structural changes in the intermediate range and variable symptom severity but finds itself as the central focus for ideal timing of MV intervention to halt progression of MR and LV remodeling (**Figure 3**) (21–24).

PATIENT SELECTION FOR INTERVENTION IN CHRONIC MR

To understand patient selection, we ought to better understand staging of MR and its relation to MR severity. Stages A and B represent mild-moderate forms of disease where periodic monitoring is recommended, whereas stages C and D represent asymptomatic and symptomatic severe MR, respectively. Further classification of stage C depends upon LV function and size (C1- LVEF >60% and LVESD ≤40 mm; C2- LVEF ≤60%; and LVESD >40 mm). Chronic severe (*primary* or *secondary*) MR is identified by the presence of a combination of the following echocardiographic criteria: central jet of MR >40% of left atrium or holosystolic eccentric MR, vena contracta ≥0.7 cm, regurgitant volume ≥60 mL, regurgitant fraction ≥50% and an

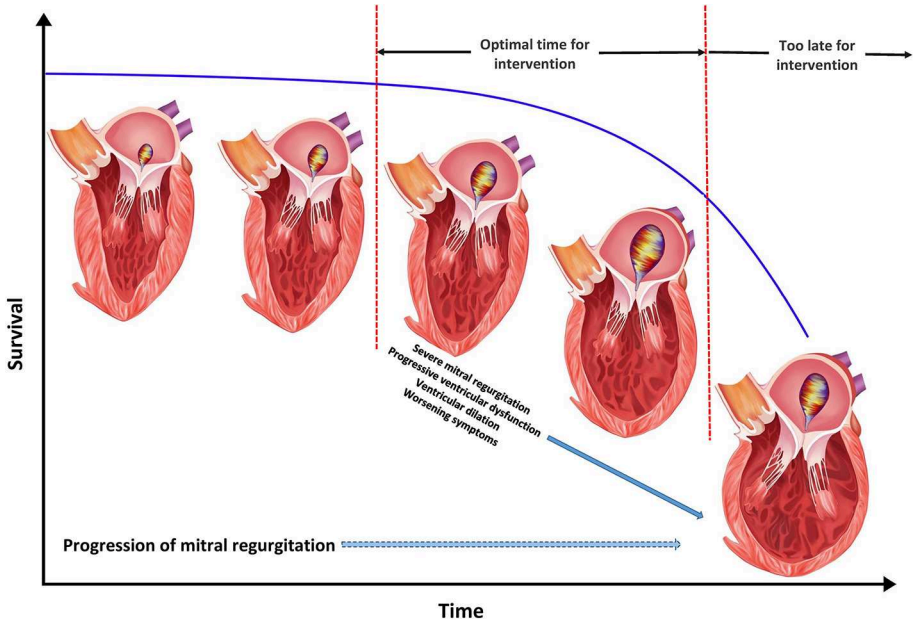

FIGURE 3 | Optimal timing for mitral valve intervention in functional mitral regurgitation (MR). The figure represents the natural history of functional MR with progression in severity of MR over time accompanied by left ventricular dysfunction, ventricular dilation, progressive symptoms, and worsening survival.

effective regurgitant orifice area (EROA) $\geq$0.40 cm^2 (20). The corresponding angiographic grade for severe MR is 3 to 4+.

The only effective therapy for severe *primary* MR is valve repair or valve replacement. Based on the 2017 update to 2014 AHA/ACC valvular guidelines, decision regarding candidacy for intervention in chronic *primary* MR is dependent on disease severity, symptom status, LV size and function, rest or exercise pulmonary hypertension, new onset atrial fibrillation, likelihood for successful repair and patient preference. Intervention for severe chronic *functional* MR is less well-studied as can be observed by the lack of a strong recommendation for mitral valve surgery among these guidelines. Guidelines are yet to be updated to reflect recent data on use of percutaneous MV therapies such as the MitraClip in functional MR, considering the potential for improvement in patient level outcomes among selected individuals with severe *functional* MR.

MANAGEMENT OF ACUTE MR

While prompt surgery is recommended in all patients with acute severe symptomatic MR, vasodilator therapies and percutaneous devices such as intra-aortic balloon pump or Impella can be used in the interim to stabilize patients in preparation for surgery (20). Valve repair is preferable over valve replacement in acute management of these patients, however the ability to repair MV is often limited by more extensive disease involving the MV apparatus (25). The role of percutaneous repair in acute MR will be discussed in the section on percutaneous therapies below.

MANAGEMENT OF CHRONIC MR

Primary MR

Medical therapy has a limited to no role in the treatment of *primary* MR, however, appropriate guideline directed medical therapy is recommended in patients with hypertension or HF with reduced ejection fraction. Surgical therapy is the treatment of choice in treatment of *primary* MR. Intervention once MR is already in the decompensated phase is accompanied with high morbidity and mortality due to recurrence of HF (26). Progression of MR severity as noted by reduction in EF to <60% or LV dilation to LVESD >40 mm is a high risk marker prior to surgery and intervention should take place before such changes occur in chronic forms of MR. The decision to intervene is complicated by the fact that some of the asymptomatic patients remain asymptomatic and stable for years whereas others develop irreversible LV systolic dysfunction. In one recent paper, the authors retrospectively followed 82 asymptomatic patients with MVP, normal ejection fraction and mild to moderate MR for a mean of 4.5 years. They found that none of the patients with mild MR progressed to severe MR, whereas 50% with moderate MR progressed to severe MR. No clinical variables or echocardiographic parameters predicted progression of disease apart from mitral annular diameter of 39.6 mm (sensitivity 100%, and specificity 63.8%)(27). The role for clinical variables such as male sex, older age, atrial fibrillation, higher weight and hypertension or echocardiographic parameters such as valvular thickening in predicting progression of disease is controversial (27–29). In summary, there are no clear predictors to which patients tend to progress, making serial clinical

and echocardiographic monitoring standard of care while on medical therapy.

MV repair is the preferred mode of therapy considering the lower operative mortality, superior long-term survival, and fewer valve related complications from bleeding and endocarditis compared to valve replacement (30, 31). Early repair has been shown to approximate outcomes in age-matched controls, extending potential benefit to asymptomatic or minimally symptomatic patients with MV disease feasible for repair at low operative risk.

Secondary MR

Pharmacologic therapy comprising of a combination of angiotensin receptor neprilysin inhibitors, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, and diuretics is recommended in the management of HF with reduced ejection fraction and severe MR (32). Use of cardiac resynchronization therapy among selected patients with LV dysfunction and dyssynchrony manifested by widening of the QRS complex on electrocardiogram is known to improve *secondary MR*. Cardiac resynchronization therapy produces marked reductions in LVESD, LVEDD and MR severity amongst responders (33, 34). Treatment of *secondary MR* includes addressing concurrent conditions such as atherosclerotic coronary artery disease in the presence of LV dysfunction via percutaneous or surgical revascularization. According to the recent valvular guidelines, a weak recommendation (Level of recommendation: Class IIb) exists for surgical intervention in patients with severely symptomatic grade 3 to 4+ *secondary MR* despite optimum guideline-directed management, treatment of coronary disease and cardiac resynchronization therapy (35). In general, neither MV replacement nor repair has been shown to improve survival in the treatment of severe *functional* MR, only symptoms. In recent randomized controlled trials of moderate or severe ischemic MR and mildly reduced ejection fraction, mitral valve repair, or chordal-sparing mitral valve replacement failed to achieve long-term favorable effects on clinical outcomes while failing to show compelling evidence for LV reverse remodeling (36, 37). At 2 years, subgroup analysis did demonstrate favorable reverse remodeling that was most evident among patients undergoing repair but had no recurrence in MR (38). On the other hand, MitraClip placement in a specific group of patients with disproportionately severe *functional* MR was shown to improve outcomes including survival as described in section below. Management of *atrial functional* MR remains understudied and its primary mechanism is related to atrial remodeling due to atrial fibrillation. Measures directed toward halting or reversing atrial enlargement in atrial fibrillation such as rhythm control or ablation strategies may be beneficial but their superiority to rate control in reversing atrial remodeling has not been studied.

Percutaneous MV Repair

Percutaneous MV repair is a minimally invasive approach to treatment of certain patients with symptomatic chronic significant MR. A multidisciplinary heart team (including general cardiologists, interventional cardiologists, cardiac surgeons, imaging specialists, HF specialists, and cardiac anesthesiologists) is recommended to evaluate and direct care among potential candidates for percutaneous valve repair. Currently, the only US Food and Drug Administration (FDA) approved device for percutaneous MV repair in *primary* and *secondary* MR is the MitraClip. Transcatheter MV repair is one of the fastest growing fields in structural heart disease intervention with constantly evolving safety and efficacy data on multiple novel device systems.

MitraClip

The MitraClip (Abbott Laboratories, Menlo Park, California, USA) is a cobalt chromium clip covered with a polypropylene fabric, has two arms and works by grasping and approximating edges of the anterior and posterior valvular leaflet segments (**Figure 4**) in patients with severe MR. It is a catheter-based technology that was designed after the surgical Alfieri technique which connects the middle segment of the anterior leaflet to the middle scallop of the posterior leaflet of a regurgitant MV (39). MitraClip received initial CE-Mark approval in Europe in 2008 and was approved by the FDA in 2013 for use in *primary* MR and 2019 for use in *functional* MR.

Procedure Technique

The percutaneous procedure is performed with the patient under general anesthesia using transthoracic, transesophageal echocardiography and fluoroscopic guidance in the cardiac catheterization laboratory. The MitraClip procedure consists of several steps following femoral venous access [(40); **Figure 4**]:

1) Transseptal puncture—In *primary* MR, the puncture site needs to be roughly 5 cm above the mitral annulus to allow sufficient catheter and clip maneuvering. In *functional* MR the puncture site needs to be more inferior and closer to the annular plane (about 3.5 cm above annular plane) since tethering of leaflets results in coaptation occurring below the plane of the mitral annulus.
2) Advancement of guide catheter and delivery system into the left atrium—A stiff guidewire is passed into the left atrium and the trans-septal apparatus is exchanged for the guide catheter. The clip delivery system is then introduced into the guide catheter and the clip is advanced into the left atrial chamber.
3) Positioning of the MitraClip into the left ventricle to just below the MV leaflets—The clip delivery system is steered until it is aligned over the origin of the regurgitant jet, its arms opened to orient it perpendicular to MV coaptation and advanced into the ventricle just below the leaflet edges.
4) Grasping the leaflet edges, confirming position and releasing the clip—The clip is closed to 120° and pulled back until the mitral leaflets are captured in the arms of the clip. The clip is incrementally closed, while its position, leaflet attachment and the degree of MR can be assessed. Prior to the final release, the clip can be reopened and repositioned if needed. After adequate reduction of MR is ensured, the clip is released from the delivery system and all catheters are withdrawn.

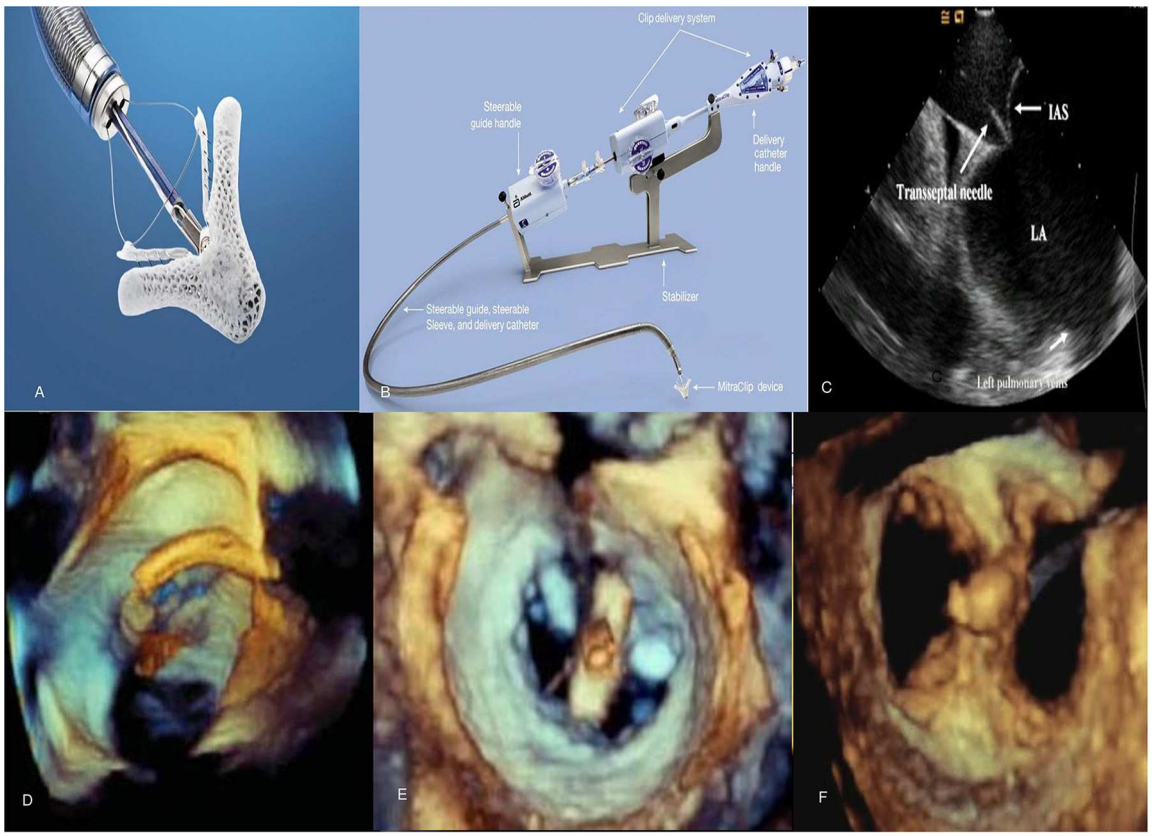

FIGURE 4 | Mitraclip system and echocardiographic images during the procedure. **(A)** MitraClip device has 2 arms and 2 grippers fabricated with metal alloys and polyester fabric. **(B)** The steerable guide catheter and clip delivery system. **(C)** Transseptal puncture using intracardiac echocardiography to enter left atrium. **(D,E)** Stepwise positioning of the MitraClip perpendicular to axis of mitral valve adjacent to the A2-P2 scallops as seen on 3D TEE. **(F)** Post-MitraClip deployment double-orifice mitral valve seen on 3D TEE. TEE, transesophageal echocardiography.

In cases with residual MR, additional clips can similarly be placed in the way of regurgitant jets while ensuring no evidence of significant *de novo* mitral stenosis. The entire procedure is performed on intravenous heparin while serially checking activated coagulation time (goal >250 s). After the clip is placed, patients are treated with aspirin 325 mg daily for 6–12 months and clopidogrel 75 mg daily for 30 days. These recommendations are based on estimated time to device endothelialization.

MV Suitability

To facilitate safe positioning of the clip, pre-procedural evaluation of certain mitral valvular anatomical criteria (EVEREST criteria) has been recommended previously to identify eligibility. Planimetered MV area $\geq$4.0 cm^2, minimal leaflet calcification in the grasping area, coaptation length of >2 mm, coaptation depth of <11 mm and in the case of degenerative disease, a flail gap of <10 mm and a flail width of <15 mm are considered favorable characteristics for MitraClip placement.

Despite the relatively stringent criteria described above, previous studies have demonstrated high rates of device success after MitraClip among patients with more complex MV anatomy including larger LV dimensions, severely reduced LV function and patients not meeting criteria for coaptation depth, coaptation length, and flail gap (41, 42). Durability of repair has been confirmed on intermediate term follow-up (1–3.5 years) depending on the study, however, a greater risk for re-intervention exists when implantation is performed beyond the above mentioned EVEREST criteria (42). In mid-2018, the US FDA approved the third generation of the MitraClip system with advanced steering, navigational and positioning clip capabilities to improve deliverability and precision of device. The new MitraClip NT_R device offers the original clip size with improved delivery system and the MitraClip XT_R device offers 3 mm longer clip arms and expands grasping reach of the device by 5 mm compared to the NT_R device (**Figure 6**). These developments have made more anatomically challenging valves favorable to successful edge-to-edge repair using the newer generation MitraClip devices.

Among contraindications to MitraClip placement are inability to tolerate procedural anticoagulation or antiplatelet agents post-procedure, active MV endocarditis, rheumatic MV disease, mitral

stenosis from any cause and thrombosis of femoral access vein, inferior vena cava or left sided intracardiac structures.

Complications of MitraClip

The risks for complications is low following MitraClip placement with rates comparable to open repair and the procedure being quite well-tolerated among recipients. Complications include access site bleeding, clip detachment from a single leaflet, device embolization, and development of mitral stenosis. In the first large scale trial evaluating MitraClip use i.e., the EVEREST II clinical trial, major adverse events of death and major stroke were similar patients receiving MitraClip and those undergoing MV surgery (43). On one hand, patients undergoing surgery needed more blood transfusions and longer mechanical ventilation whereas MitraClip implantation was associated with greater onset of new atrial fibrillation and acute renal failure. Rate of 30-day complications is usually in the range of 15–19% following such transcatheter MV repair (43, 44). Bleeding is largely peri-procedural from the vascular access site for MitraClip due to its large sheath size. Partial clip detachment is most common in the first year post-procedure but occurs in <5% cases. Clip embolization and complete detachment or hemodynamically significant mitral stenosis are rare. Risk for endocarditis involving the MitraClip is unclear since most data comes from case reports and use of peri-procedural antibiotic prophylaxis among recipients of MitraClip is controversial (45).

Clinical Application

Chronic Primary MR

The 2017 focused update of the 2014 AHA/ACC valve guidelines suggested use of MitraClip in chronic severe *primary* MR (3 to 4+) among those who were highly symptomatic (New York Heart Association class III to IV) despite optimal guideline-directed medical therapy (stage D), had favorable anatomy, reasonable life expectancy and a prohibitive surgical risk due to comorbidities (**Table 4**). For patients with *primary* MR who met all criteria, the next step involves referral to the Heart Team for feasibility and potential risk vs. benefit from procedure. Most of these recommendations were made mainly in light of data from the EVEREST II trial.

In the EVEREST II trial, 279 patients with 3+ to 4+ MR were randomized in 2:1 fashion to undergo either percutaneous repair, i.e., MitraClip device (184 patients) or mitral-valve surgery (95 patients) (43). Among patients undergoing MV surgery, 86% underwent MV repair and the rest underwent replacement. At least three of the following echocardiographic criteria were used to define moderate-severe (3+) or severe (4+) MR: (i) regurgitant color flow jet that was central and large (>6 cm^2 or >30 percent of left atrial area) or smaller if eccentric, encircling the left atrium, (ii) pulmonary vein flow showing systolic blunting or systolic flow reversal, (iii) vena contracta ≥0.5 cm in the parasternal long axis view, (iv) regurgitant volume ≥45 ml/beat, (v) regurgitant fraction ≥40 percent, and (vi) regurgitant EROA ≥0.30 cm^2. All patients were required to have a primary regurgitant jet from malcoaptation of the middle segments of the anterior and posterior leaflets at recruitment. ∼3/4ths of the patients who made it into the study had *degenerative* MR.

TABLE 4 | Factors that determine prohibitive surgical risk among patients with primary MR undergoing MitraClip evaluation.

Prohibitive surgical risks to mitral valve surgery
30-day Society of Thoracic Surgeons (STS) predicted operative mortality risk score of ≥8%
Porcelain or highly calcified aorta
Patient frailty
Severe liver disease
Severe pulmonary hypertension
Right ventricular dysfunction with severe tricuspid regurgitation
Others- chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia

The primary composite end point for efficacy was freedom from death, from surgery for MV dysfunction and from ≥3 grade residual MR. At 12-months, the end point was more frequent in the surgery group (73 vs. 55%) due to the higher rate of subsequent surgery for MV dysfunction in the MitraClip arm (20 vs. 2%). Mortality and ≥3 grade residual MR were similar in the two groups at ≈6 and ≈20%, respectively. Major complications at 30-days were higher in the surgical arm largely from a higher rate of transfusing ≥2 units of blood among patients undergoing surgery. More recently published 5-year data shows that patients who received MitraClip continued to have higher rates of repeat surgery and residual MR compared to the surgical arm, without any difference in overall mortality [(46); **Table 5**]. These data are reassuring for safety of MitraClip implantation in *primary* MR, but highlights the need for appropriate patient selection since more than a quarter of the patients needed repeat surgery at 5-years post-MitraClip placement. The majority of repeat surgery was still performed during the first year of follow up, lending credibility to the durability of a successful MV repair using the MitraClip.

The quality of life benefits seen with MitraClip early on persisted on subsequent follow-up of the patients enrolled in EVEREST II with the proportion of patients with NYHA class III/IV symptoms decreasing to 5.7% at 4 years from 45% at baseline. Such improvement in quality of life metrics and reduction in HF hospitalization was present within the subsection of patients at prohibitive risk of MV surgery (49). An additional benefit of timely MV intervention was noted in the form of LV reverse remodeling and reduction in LV and left atrial volumes from successful reduction in MR using MitraClip according to the initial EVEREST II trial and subsequent data (50). Studies examining commercial use of MitraClip in predominantly *primary* MR have reported high procedural success with <3 grade residual MR of >90%, hospital mortality rate <3% and overall 30-day serious complication rates of 10 to 15% (51, 52). Based on these initial results, continued overwhelmingly favorable outcomes with MitraClip in *degenerative* MR over time and advancements in cardiovascular imaging enabling better

TABLE 5 | MitraClip trials on treating patients with severe mitral regurgitation.

Study	Design	Comparison groups	Etiology for MR	Study endpoints
Feldman et al. EVEREST II Trial 5-Year Results (46)	Prospective, multi-center, randomized controlled trial	2:1 MitraClip ($n = 178$) vs. MV surgery ($n = 80$)	73% primary MR, 27% functional MR	44.2 vs. 64.3% ($p = 0.01$)* 12.3 vs. 1.8% ($p = 0.02$)§ 27.9 vs. 8.9% ($p = 0.003$)€ 20.8 and 26.8% ($p = 0.4$) ¥
Stone et al. COAPT Trial (47)	Prospective, multi-center, randomized controlled trial	1:1 MitraClip ($n = 302$) vs. medical therapy ($n = 312$)	100% functional MR with LV dysfunction	35.8 vs. 67.9% ($p < 0.001$)** 5.2 vs. 53.1% ($p < 0.001$)§§ 29.1 vs. 46.1% ($p < 0.001$)¥ ¥
Obadia et al. MITRA-FR Trial (48)	Prospective, open label, multi-center, randomized controlled trial	1:1 MitraClip ($n = 152$) vs. medical therapy ($n = 152$)	100% functional MR with LV dysfunction	54.6 vs. 51.3% ($p = 0.53$)*** 48.7 vs. 47.4% ($p > 0.05$)§§§ 24.3 vs. 22.4% ($p > 0.05$) ¥¥¥

Composite endpoint: freedom from death, surgery, or 3+ or 4+ MR according to as treated analysis.
§*Rates of residual ≥3+ MR.*
€*Rate of repeat surgery.*
¥*Five-year mortality rates according to as treated analysis.*
***Heart failure hospitalization within 24 months.*
§§*Rate of residual ≥3+ MR at 12 months.*
¥¥*Death from any cause at 24 months.*
****Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months.*
§§§*Unplanned heart failure hospitalization at 12 months.*
¥¥¥*Death from any cause at 12 months.*

anatomical characterization, an argument is made for wider clinical application of the device among patients at less than prohibitive risk of surgery. Such patient selection should occur on the basis of individualized decision-making and the Heart Team approach.

Chronic Secondary MR

Two separate randomized controlled trials compared the efficacy of percutaneous MV repair using MitraClip to medical therapy among patients with significant *secondary* MR and underlying LV abnormality [**Table 5**; (47, 48)]. These studies found conflicting results which can be explained to a certain degree by differences in their study design and patient enrolment (**Figure 5**).

Cardiovascular outcomes assessment of the mitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation (COAPT Trial)

The study enrolled 614 patients with LV dysfunction (EF 20–50%) and moderate-to-severe or severe *secondary* MR who remained symptomatic despite the use of maximal doses of medical therapy. Among those enrolled in the trial, 302 patients were assigned to the MitraClip group (and guideline directed medical therapy) and 312 patients to the control group receiving just guideline directed medical therapy. The study excluded patients with LVESD >7 cm. Placement of MitraClip was successful in 98% of the treatment arm with 95% of the patients with echocardiograms at discharge showing <3 grade residual MR. Similarly at 12-months, severity of MR was <3 grade in 94.8% compared to 46.9% in the treatment and control arms, respectively. Clinical study endpoints were significantly improved in the treatment arm compared to controls, such as 2-year mortality (29.1 vs. 46.1%) and 2-year HF hospitalization (35.8 vs. 67.9% per patient year). Interestingly, there was no difference in mortality at 12-months between study groups. Additional measures of quality of life such as NYHA functional class I or II (72.2 vs. 49.6%) and change in the mean Kansas City Cardiomyopathy Questionnaire Score (+12.5 vs. −3.6 points) were more favorable among patients receiving MitraClip compared to the medical arm. There was evidence of reverse remodeling at 12-months within the treatment arm compared to control (mean change in LVEDV from baseline −3.7 ml vs. +17.1 ml, respectively). At 12-months, 3.4% of patients experienced a MitraClip related complication (composite of single leaflet attachment, device embolization, endocarditis or mitral stenosis needing surgery, left ventricular assist device implantation, cardiac transplantation, and device complication requiring non-elective cardiovascular surgery).

Percutaneous repair with the mitraClip device for severe functional/secondary mitral regurgitation (MITRA-FR trial)

The trial enrolled 304 symptomatic patients with LV dysfunction (EF 15–40%) and moderate to severe *secondary* MR to either percutaneous mitral-valve repair plus medical therapy ($n = 152$) or medical therapy alone ($n = 152$). Placement of MitraClip was successful in 95.8% of the treatment arm with 91.9% of the patients showing <3 grade residual MR at discharge and ≈82% at 12-months. Mortality (24.3 vs. 22.4%) and unplanned HF hospitalization (48.7 vs. 47.4%) at 12-months were similar in the device and control arms. Patient NYHA functional class I or II (range ≈65–70%) and mean EQ-5D quality of life score (60.8 vs. 58.6) ware similar between the treatment and control arms at 12-months. Improvement in NYHA functional class occurred in both arms compared to their baseline. Differences in median LVEDD, LVEDV, LVESD, and LVESV were minimal in both study groups at 12-months from baseline. Within the intervention group, 14.6% of patients experienced a MitraClip related complication (composite of device implantation failure, significant hemorrhage or vascular event, atrial septal lesion,

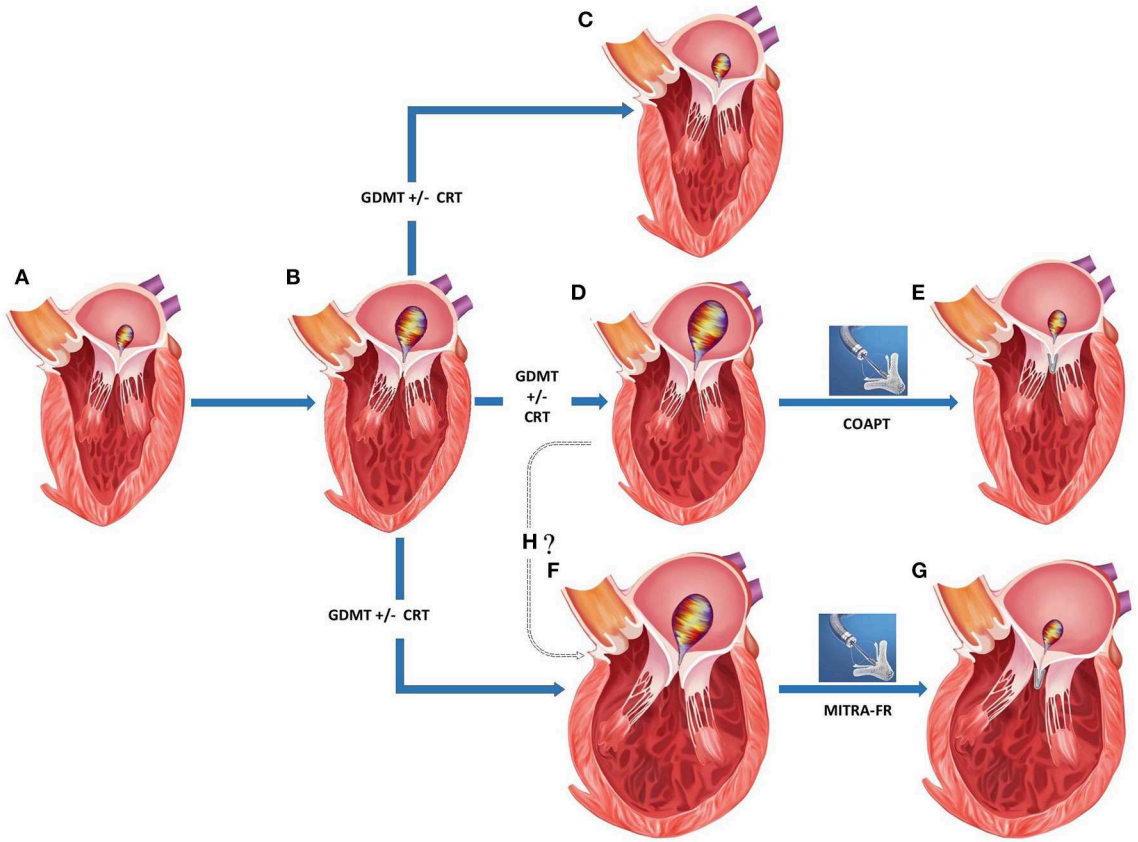

FIGURE 5 | Appropriate patient selection for percutaneous transcatheter mitral valve replacement in severe functional mitral regurgitation (MR). **(A)** Normal left ventricular (LV) dimensions with mild MR. **(B)** Progression to moderate regurgitation and mild LV dysfunction. **(C)** Left ventricular recovery with mild MR following medical management. **(D)** Progression of LV dysfunction with mild-moderate LV dilation and severe MR despite medical management. **(E)** Post-MitraClip improvement in LV function, LV reverse remodeling, and reduction in residual MR. **(F)** Progression of LV dysfunction with moderate-severe LV dilation and severe MR despite medical management. **(G)** Post-MitraClip no change in LV size or function despite reduction in residual MR. **(H)** Whether structural changes in **(D,F)** represent separate phenotypes or a continuation on the spectrum of increasing disease severity. GDMT, guideline directed medical therapy; CRT, chronic resynchronization therapy.

cardiogenic shock requiring inotropes, cardiac embolism, tamponade, and urgent conversion to cardiac surgery).

COAPT vs. MITRA-FR

Despite the overall similarities in trial design and high overall event rates signaling enrollment of a high risk patient population in both trials, there were several important differences that may have led to the disparate results (53, 54). One of the key variations was the criteria used for defining severity of MR. MITRA-FR used the 2014 ACC/AHA and ESC valvular guidelines where more modest degrees of MR were misclassified as severe *secondary* MR. We have represented several of the relevant baseline differences between device arms in the two trials as displayed in **Table 6**.

To summarize these differences, compared to patients in MITRA-FR, those in COAPT had

i) More severe degrees of MR,
ii) Less remodeled LV,
iii) Disease refractory to medical therapy resulting in lower potential for improvement among controls,
iv) HF disease that could be attributed to valvular dysfunction over ventricular dysfunction,
v) Improved procedural efficacy and less residual (grade <3) MR and
vi) Longer follow up in COAPT since differences emerged beyond the 12-month mark.

Additional trial information on guideline directed medical therapy, dose titration and CRT optimization would shed more light on the differences between the two trials. Confirmation of the clinical responsiveness to MitraClip implantation of proportionate vs. disproportionately severe MR could be confirmed by combining data from these trials and identifying response to specific disease phenotypes. More longitudinal data from MITRA-FR and publication of well-designed randomized control trials with distinct morphological entry criteria will pave the way for furthering our understanding on percutaneous MV repair in *secondary MR* and assist in exploring timing of such intervention. Whether coupling clip placement with other percutaneous procedures directed toward optimization

TABLE 6 | Baseline characteristics in COAPT and MITRACLIP trials (device arms).

Variable	COAPT MitraClip arm ($n = 302$)	MITRA-FR MitraClip arm ($N = 152$)
Clip implantation success rate (implanted/attempted)	98% (287/293)	95.8% (138/144)
Inclusion criteria for degree of secondary MR*		
Regurgitant volume	>45 ml	>30 ml
Effective regurgitant orifice	≥0.3 cm^2	>0.2 cm^2
Grade of MR	≥3+	≥3+
Age – years (mean ± SD)	71.7 ± 10.1	70.1 ± 10.1
Male sex	66.6%	78.9%
NYHA class III/IV	57%	63.1%
Previous myocardial infarction	51.7%	49.3%
Previous atrial fibrillation	57.3%	34.5%
Type of Cardiomyopathy		
Ischemic	60.9%	62.5%
Non-Ischemic	39.1%	37.5%
Medications at baseline		
ACEI, ARB or ARNI	71.5%	83.0%
Beta-blocker	91.1%	88.2%
Mineralocorticoid receptor antagonist	50.7%	56.6%
Diuretic	89.4%	99.3%
Oral anticoagulant	46.4%	61.2%
Previous cardiac resynchronization therapy	38.1%	30.5%
B-type natriuretic peptide level (pg/ml)	1,014 (Mean)	765 (Median)
≥2 clips implanted	61.8%	54.3 %
Effective regurgitant orifice area (cm^2)	0.41 ± 0.15	0.31 ± 0.1
Mean left ventricular end-diastolic volume (ml)¥	194	254
Left ventricular ejection fraction (%)	31.3 ± 9.1	33.3 ± 6.5

**Confirmed at an Echocardiographic Core Laboratory before enrollment corresponding to moderate-to-severe or severe MR.*

¥Calculated left ventricular end-diastolic volume in MITRA-FR arm based on indexed volume 136.2 ml/m^2.

MR-mitral regurgitation, SD, standard deviation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARNI, Angiotensin Receptor-Neprilysin Inhibitor.

of other anatomical abnormalities within the mitral apparatus (such as chordal replacement, altering ventricular, or atrial geometry among others) alters the disease course of severe MR remains to be studied and has potential to expand the patient pool that would benefit from such a combination procedure (55).

Proportionate vs. Disproportionate MR

Secondary MR seems to represent a rather diverse group where in some situations, the MR can be explained by morphological changes affecting the LV such as global dilation and others when remodeling changes within the LV affect the MV apparatus to a greater degree than global LV function (56). In a recent paper, Grayburn and Packer described how EROA is dependent on both the LVEDV and LVEF, such that among patients with reduced LVEF ≈30% and LV dilation (LVEDV 200–250 ml), an EROA of 0.2 cm^2 is common and reflects only a moderate degree of MR instead of severe (57). In such cases, MV intervention was unlikely to benefit as patients were considered to have a proportionate degree of MR to LV dilation. The authors raised a framework in which the severity of MR was identified by integrating the EROA, LVEDV, and LVEF, and responders to mitral valve intervention were felt to have an unexpectedly severe and disproportionate degree of MR to the degree of LV dilation. Responders to mitral valve intervention were more likely to have a less-dilated LV and relatively larger EROA, where the ratio of EROA to LVEDV was higher among patients with disproportionate MR than those with proportionate MR (**Figure 5**).

Unresolved Questions

With two randomized trials of MitraClip in *functional* MR yielding differing results and despite attempts to reconcile the differences to pinpoint responders, there remain several unknowns.

- It is unclear if the phenotypical varieties of MR with disproportionately severe and proportionately severe MR represent disease on a spectrum of increasing severity and whether early intervention would prevent progression to the latter more advanced disease (**Figure 5H**). As an alternative theory, it is conceivable that these may exist as independent entities and in patients where cardiac remodeling disproportionately involves the muscle supporting MV, malcoaptation results in MR. Such MR is actually more responsive to MitraClip implantation and the result is an improvement in clinical outcomes with LV reverse remodeling.
- MitraClip placement and acute reductions in MR provides room for uptitrating well-validated heart failure medical therapies, and the gains from such medical optimization may play a role and will become apparent over time.
- Objective measurement of MR severity relies heavily on Proximal Isovelocity Surface Area Calculation (PISA) from flow convergence on 2-dimensional echocardiography. Existing data suggests that regurgitant jets in *functional* MR are often eccentric with asymmetrical flow convergence patterns inadequately visualized by the current standard in clinical practice i.e., 2-dimensional echocardiography. The EROA measurement may be more accurate using 3-dimensional imaging techniques with greater accuracy in recognition of the PISA radius (58). Direct cardiac imaging techniques such as computed tomography and magnetic resonance imaging have the ability to directly measure the EROA and regurgitant volumes (59). Whether severity parameters for MR can be used interchangeably across the newer modalities needs further testing prior to more widespread clinical use.
- Prior MitraClip trials did not enroll patients with significant tricuspid regurgitation and markedly elevated pulmonary arterial pressures. Innovations in percutaneous tricuspid valvular interventions may enable future interventions on both atrioventricular valves during the same or in a staged setting to maximize benefit (60).

As more prospective and retrospective analyses testing several of these previously mentioned hypotheses and theories come forward, our ability to understand and manage *functional* MR is destined to evolve.

Acute MR

There is limited experience with transcatheter MV repair in treatment of acute MR. Successful placement of MitraClip has been described in some patients developing severe MR following acute myocardial infarction with acute improvement in MR severity and symptoms (61). In one case series of 5 patients post-AMI, MitraClip was placed with marked symptomatic improvement and reduction in pulmonary pressures with <3+ residual MR in all patients. MitraClip was successfully placed with immediate reduction in MR severity and pulmonary pressures. One patient died of multi-organ failure within 1 week of the procedure. The other four patients were alive after 1 year with improved New York Heart Association (NYHA) functional class. While none of the patients in this case series had papillary muscle rupture accompanying acute severe MR, reports do exist on treating acute MR with MitraClip in the presence of posterior papillary muscle rupture (62). Widespread evidence for the benefit of percutaneous approach over surgical intervention and its longevity is still lacking and surgical intervention remains the most appropriate option in most patients with acute MR. Percutaneous intervention remains a tool in high surgical risk patients and requires assessment by a multidisciplinary team. Timing of such intervention remains unclear with some patients needing respiratory support in addition to short term mechanical circulatory support in the interim while awaiting decision and treatment.

Emerging Technologies for Percutaneous Mitral Intervention

A considerable number of patients with severe MR do not meet anatomic criteria for MitraClip repair. Several other devices in the percutaneous arena possess potential applications in chronic MR permitting a customized strategy to mimic the traditional surgical interventions, in an individual or combination approach (**Figure 6**).

Currently there are four primary transcatheter approaches (**Table 7**)

- Edge-to-edge clip (Alfieri-type) repair (MitraClip, PASCAL TMVr system),
- Percutaneous MV annuloplasty indirectly via the coronary sinus or directly from retrograde LV access (Carillon, Cardioband, Millipede, Mitralign, ARTO systems),
- Chordal replacement (NeoChord, Harpoon Cords) and
- Transcatheter MV replacement (Sapien-XT, Melody, CardiaAQ, Caisson valve, etc.).

Of these transcatheter techniques, only the former two have viable well-tested percutaneous access MV repair strategies. Most the upcoming technology on either chordal replacement or MV replacement uses primarily transapical access via lateral mini-thoracotomy.

Edge-to-Edge Clip Repair

- **PASCAL Transcatheter MV Repair:** The PASCAL TMVr (Edwards Lifesciences, Irvine, CA) system is designed to overcome shortcomings of the MitraClip system by facilitating easy steering within the left atrium, larger implant size, broader paddles with central spacer within device to reduce MR by maximizing leaflet coaptation, ability to grasp individual leaflets and implant elongation to promote safe subvalvular maneuvering (63). Placement of the device occurs via transvenous access (femoral) and transseptal approach similar to the MitraClip. In its first human study, the PASCAL TMVr was studied in 23 patients with symptomatic severe *degenerative*, *functional* or *mixed* etiology MR (NYHA functional class III to IV) and patients were deemed high to inoperable surgical risk (64). Patients were not considered candidates for MitraClip repair either due to anatomical complexity (short posterior leaflet, large malcoaptation area, severe annular dilatation >61 mm) or lack of an approved indication for use. Procedural success was obtained in 22/23 patients (96%), residual MR was <3 grade in 96% patients and reduction in NYHA functional class ≤II grade occurred in 95% of the cases. By 30-days post-implantation, three patients (13%) had died. Direct procedure related complications occurred in two cases (9%) from a minor bleeding event and transient ischemic attack, respectively. The device expanded patient eligibility for repair especially in case of short posterior leaflets and larger flail gaps and needs additional data on durability and future head-to-head comparisons with newer generations of the MitraClip device.

Indirect Annuloplasty Devices

- **CARILLON Mitral Contour System:** The CARILLON Mitral Contour System (Cardiac Dimensions, Inc., Kirkland, Washington) combines a proprietary, implantable device with a percutaneous catheter delivery system through transjugular venous access to treat *functional* MR. The device is an indirect annuloplasty device composed of two self-expanding nitinol anchors with a connecting curvilinear segment and is positioned with its proximal anchor at the coronary sinus ostium, distal anchor within the great cardiac vein. Upon deployment the device plicates the tissue next to the MV annulus reducing mitral annular dilation and degree of MR by bringing the anterior and posterior leaflets closer. Coronary angiography is also performed to evaluate for left circumflex-obtuse marginal arterial system compression following deployment due to its close proximity. Current technology allows either recapture and repositioning of device implant during same procedure or recapture and removal of original device followed by new device implantation when needed. Such manipulation becomes possible due to its benign design and availability in multiple sizes.

  Initial studies of the CARILLON Mitral Contour System, AMADEUS, and TITAN showed improvement in symptoms, quality of life, severity of MR and evidence for LV reverse remodeling when used to treat symptomatic high risk patients with FMR (65, 66). The earlier generation device

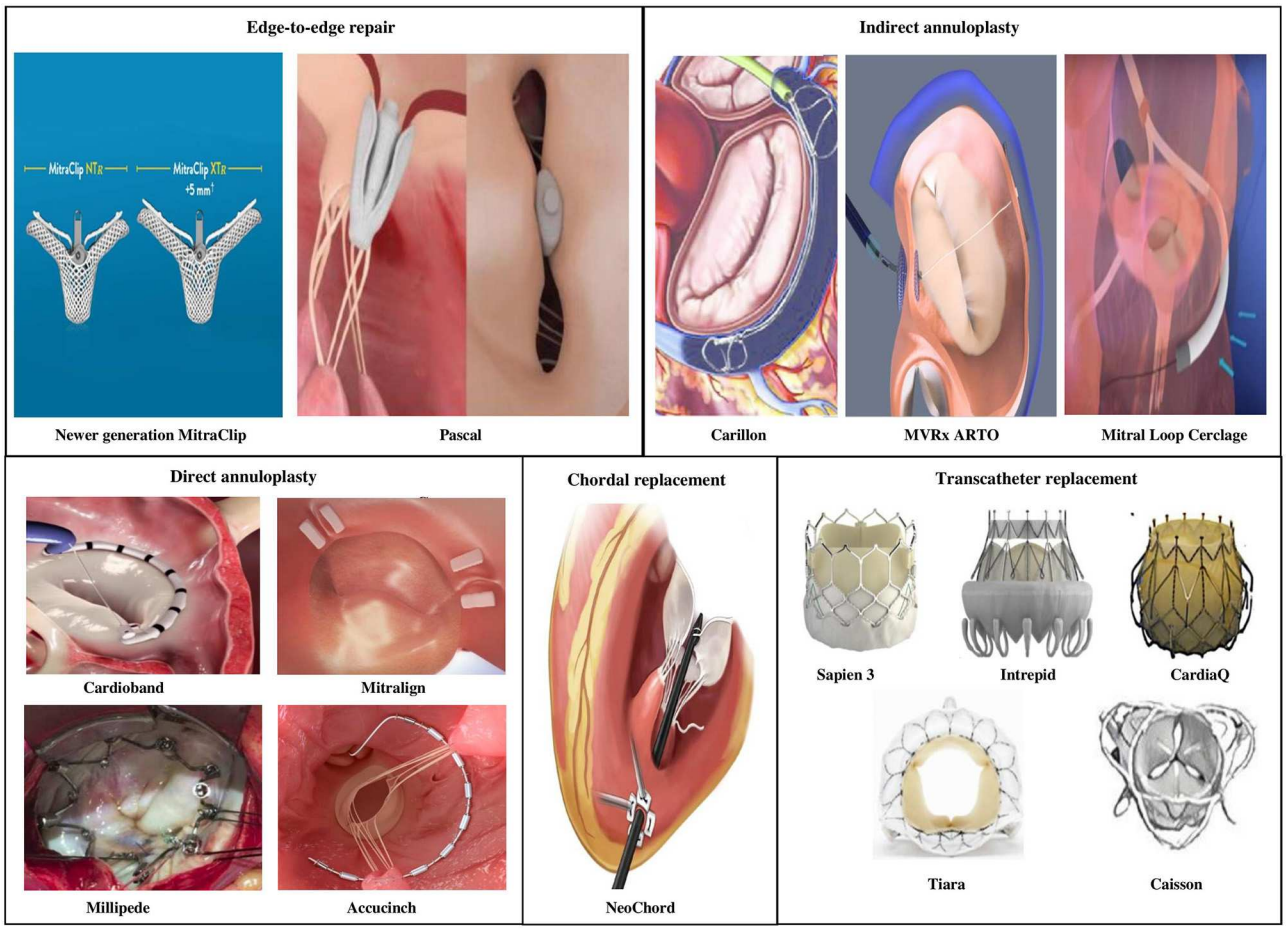

FIGURE 6 | Newer transcatheter mitral valve interventions in patients with mitral regurgitation.

had a reasonable safety profile, but asymptomatic wire-form fractures were seen at the level of the high strain proximal anchor locking mechanism in the Carillon device in 25% of cases. TITAN II was a prospective, single-arm, multinational safety study conducted in order to test the newer generation modified Carillon device designed to reduce the strain in the wireforms of the proximal anchoring segment (67). There was a single device fracture 1/36 (2.8%) attributed to incorrect placement of a recaptured/redeployed device. The primary end point of 30-day major adverse event rate was 2.8% due to one incidence of non-arrhythmic sudden death occurring at 17-days post-procedure. The 1-year mortality was 23% (7 of 30 patients) and no deaths were adjudicated to be device related. From the efficacy standpoint, TITAN II showed similar clinical and echocardiographic benefits as in TITAN with reduction in MR, mitral annular dimension, improvement in NYHA functional class and a trend toward reduction in ventricular size suggestive of reverse remodeling. The modified Carillon device used in the TITAN II study is currently being evaluated in a multicenter blinded randomized control trial (REDUCE FMR trial).

- **ARTO device: The MVRx ARTO transcatheter annular reduction therapy** (MVRX, Inc., Belmont, California) is an indirect annuloplasty system that includes transvenous delivery of 2 anchors: one through the interatrial septum, the other to the coronary sinus and acts by reducing the anteroposterior diameter of the mitral annulus. Procedure is performed using general anesthesia. The MV RepaIr Clinical (MAVERIC) trial program is a prospective single arm group of studies evaluating safety and performance of the device in *functional* MR with promising early results in the first 11 of a total of 31 patients (68). Publication of full data is awaited.
- **Mitral Loop Cerclage Catheter System:** In the mitral loop cerclage (Tau-PNU Medical Co, Ltd., Pusan, Korea) procedure, both the femoral vein and left subclavian vein (via a pacemaker-type pocket) are accessed. The cerclage is accomplished by using a guidewire to enter the coronary sinus and great cardiac vein, crossing the interventricular septum from the anterior interventricular vein into the right ventricle, snaring this wire from the right ventricular outflow tract and forming a loop around mitral annular plane. The guidewire is exchanged for a tension device containing an

TABLE 7 | Emerging transcatheter mitral valve repair technologies for mitral regurgitation with data in humans.

Device	Access	Transseptal puncture	Etiology	Mechanism
Edge-to-edge repair				
MitraClip	Femoral vein	Yes	PMR, FMR	Clip based edge to edge repair. Creation of a double orifice mitral valve to reduce regurgitation
PASCAL	Femoral vein	Yes	PMR, FMR	
Indirect Annulopasty				
Carillon	Internal jugular	No	FMR	Reduction in mitral regurgitation through reduction in mitral valve annulus through coronary sinus. Due to its proximity to left circumflax artery, coronary artery compression is a known complication
MVRx ARTO	Internal jugular and femoral vein	Yes	FMR	
Mitral Loop Cerclage	Subclavian vein + femoral vein	No	FMR	
Direct Annulopasty				
Cardioband	Femoral vein	Yes	FMR	Direct attachment to and reduction in mitral valve annulus to reduce mitral regurgitation. Placement may be within the left ventricular wall in case of certain devices
Mitralign	Femoral artery	No	FMR	
Accucinch (Ventriculoplasty)	Femoral artery	No	FMR	
Millipede	Femoral vein	Yes	FMR	
Chordal Replacement				
NeoChord	Transapical off-pump	No	PMR	Attachement of false chordae to mitral leaflets in cases of leaflet prolapse or flail to reduce mitral regurgitation
Transcatheter valve replacement				
Endovalve, Tiara, Fortis, Tendyne, etc.	Transapical off-pump	No	PMR, FMR	Transcatheter bioprosthetic mitral valve placement either as valve in valve, valve in ring or valve in native mitral annulus to reduce mitral regurgitation
Sapien-XT	Femoral vein	Yes	Bioprosthetic valve dysfunction	
CardiaAQ, Caisson, Cardiovalve	Femoral vein +/– femoral artery	Yes	PMR, FMR	

PMR, primary or degenerative mitral regurgitation; FMR, secondary or functional mitral regurgitation.

integrated coronary artery protection element preventing coronary compression and tension is applied to compress the mitral annulus and improve leaflet coaptation. The tension locking device is embedded in the left subclavicular pocket. The procedure is performed either under general anesthesia or moderate sedation. The first in human study attempted the procedure in 5 patients, was successful in 4/5 patients but aborted in one due to unfavorable anatomy (69). The device resulted in immediate reduction in MR that was sustained upto 6-months and reduced left atrial and LV chamber volumes over time. Device related complications were coronary artery occlusion, new bundle branch block and need for a repositioning procedure. While several breakthroughs are being made in the field of indirect annuloplasty to reduce *functional* MR, unfavorable coronary sinus and branch vein anatomy seems to play a major role in limiting procedural feasibility in a significant proportion of patients depending on device.

Direct Annulopasty Devices

- **Cardioband:** The Cardioband device (Edwards Lifesciences, Irvine, CA) delivers direct sutureless anchors around the mitral annulus to connect the annuloplasty device. The cardioband system enables adjustable septo-lateral diameter compression, reducing MV annulus size and severity of MR. In the largest multicenter study of 60 patients with moderate to severe *secondary* MR who underwent Cardioband implantation, early results raised issue with device design leading to device modification half way through the study (70). Anchor disengagement was observed in 10 patients, resulting in device inefficacy in five patients but most (9/10 anchor disengagement) occurred prior to device modification. There were no device related deaths and 1-year overall survival was 87%. While severity of MR improved in most patients at 1-year, worsening of MR was still noted in 1/5 patients. Quality of life markers, exercise capacity and NYHA functional status improved at 1-year compared to baseline in most patients. The 2-year (unpublished) results continue to reveal sustained reduction in septolateral diameter, MR severity and patient quality of life.
- **Mitralign Annuloplasty system:** The Mitralign system (Mitralign, Tewksbury,Massachusetts) involves transfemoral access using a deflectable catheter which is introduced into the LV and directed toward the posterior annulus. Using a combination of wires and catheters, polyester pledgets are placed across the annulus into the left atrium first at the P1/P2 scallops followed by the P2/P3 scallops of posterior mitral annulus if needed. One to two pairs of pledgets are plicated, locked and the result is a reduction in MV annular diameter. The device has been tested in a prospective, multicenter single-arm feasibility study where 45 patients underwent procedure (71). There were no intraprocedural deaths or conversion to surgery, but pericardial tamponade occurred in 4 (8%) patients. Exclusion of LVEDD <5 cm and second generation catheter systems have decreased the risk of tamponade. Within 6-months, all-cause mortality was 12.2%, 7 (17%) patients

underwent MitraClip placement and one patients received non-emergent MV surgery. Improvement was noted in MR severity in 50% of the patients with worsening in 15.4% cases, with greater trend for improvement in those who received 2 pledgets. HF symptoms and 6-min walk test improved at 6-months from baseline. It is not currently available for commercial use.

- **Newer devices**: The Millipede IRIS ring is a semirigid "zigzag" shaped annuloplasty ring, with eight helical stainless steel anchors that anchor directly into the mitral annulus. Device has eight tensioning sliders that can be used to actuate the device and reduce the annulus size (72). The AccuCinch Ventricular Repair System (Ancora Heart, Santa Clara, CA) uses a retrograde arterial mechanism to implant a series of adjustable anchors within the LV wall tethered by a cable below the mitral valve annulus. The cable is tightened to cinch the left ventricular wall, reducing ventricular size and consequently mitral annulus, thus succeeding in lowering regurgitant volume. Unlike other systems within this section, the AccuCinch system represents more of a ventriculoplasty than direct annuloplasty due to its direct support to and placement within the left ventricular myocardium; consequently, this device is current being tested in heart failure patients with dilated left ventricles but without significant valvular lesions. Prospective clinical data is awaited on these devices and studies are underway.

Chordal Replacement

The Neochord is a transcatheter surgical off-pump mitral repair procedure which implants artificial cords into the mitral valve and is performed under general anesthesia in a standard cardiac operating theater. Access to the LV is obtained through a left lateral mini-thoracotomy and transapical access. Several studies on the safety and efficacy of such a transcatheter strategy in reducing MR have been published (73, 74). Another similar device is the Harpoon MV Repair System that anchors artificial cords on the flaps to take the place of the natural cords via transapical off-pump surgical technique using transcatheter technology. Chordal replacement is more commonly used in *degenerative* MV disease and no current transvenous or transarterial systems mimic either of these techniques.

Transcatheter MV Replacement

There have been several studies demonstrating feasibility of transcatheter MV replacement using a bioprosthetic valve for symptomatic MR especially among high risk surgical patients (75, 76). These new transcatheter valves are mostly implanted via minimally invasive surgical approach and transapical access but recent literature sheds light on promising new percutaneous transseptal delivery systems (77). We have directed our focus below primarily to the percutaneous non-surgical implantable valvular systems. As more feasibility data becomes available, these results show favorable reduction in MR severity and improvement in patient symptoms with an acceptable early mortality rate among high surgical risk populations. Challenges remain due to complex mitral anatomy, proximity to LV outflow tract, valve positioning, mitral annular calcification, large delivery systems and valve size, device thrombosis, and hemolysis in addition to complications from transapical access.

Complementing the significant strides achieved in aortic valve implantation, techniques required to perform mitral transcatheter implantation have progressed quickly. The SAPIEN-XT (Edwards Lifesciences, Irvine, CA) and Melody valve (Medtronic, Minneapolis, MN) have shown excellent success in percutaneous valve-in-valve and valve-in-ring implantations in the mitral position but are not recommended in native regurgitant MVs (78, 79). Placement of bioprosthetic MV through vascular access has been challenging primarily due to the larger device size in the mitral position, an asymmetric D-shaped dynamic annulus and lack of adequate support from the native MV annulus. While clinical data is scant, percutaneous mitral replacement into native valves has been successful in certain cases. The CardiaAQ (CardiAQ Valve Technologies, Inc. Winchester, MA) valve has leaflets made from porcine pericardium onto a nitinol self-expanding stent and was delivered transseptally in an 86-year old high risk patient with improvement in MR (80). Four separate vascular accesses were obtained, 2 in the femoral artery and 2 in the femoral vein to facilitate the complex procedure using multiple catheters and delivery systems. The patient later died on day 3 post-procedure from non-device related complications. In a first of its kind study, PRELUDE studied feasibility of transfemoral access and transseptal delivery of the Caisson transcatheter MV replacement (LivaNova, Maplegrove, MN) in humans. While the results have not been published, statements released from the company indicated encouraging positive outcomes with sustained valvular performance and improved quality of life in patients post-replacement. The INTERLUDE CE-Mark clinical trial has been launched using this device to be performed at sites across North American and Europe. In a first in human study, 10 patients underwent percutaneous transcatheter mitral valve replacement via transseptal approach for severe MR of varying etiology (4 *degenerative*, 4 *functional*, 2 *mixed*) and high surgical risk (77). The delivery system comprises a nitinol dock encircling the chordae tendineae, and a balloon-expandable bioprosthetic valve. The device was successfully implanted in 9 of the 10 patients. Residual MR was mostly trivial ($\leq$1+ MR) in all nine patients that underwent valve replacement with a minimal transmitral gradient. At 30 days, there was no death, stroke, myocardial infarction, re-hospitalization, left ventricular outflow tract obstruction, device migration, embolization, or conversion to mitral surgery. Complications reported were a case of pericardial effusion precluding valve placement and one case of paravalvular regurgitation managed with a percutaneous closure device.

As several companies are developing percutaneous systems for delivering bioprosthetic MVs, trends indicate that the coming 5-years will see rapid advancements in the field of percutaneous MV replacement and more human data will become available from ongoing studies (81). Within the next decade, it is certainly plausible that we will see studies among low to intermediate surgical risk populations as transcatheter techniques evolve and achieve greater success.

CONCLUSION

Heart Team sets the foundation for delivering the best quality of care to patients with valvular heart disease by leveraging the expertise of its members and enhancing collaboration. Technical and more so technological advances have forged the field of microinvasive cardiac valvular operation and amplified the role of a Heart Team approach (82, 83). These procedures include a variety of percutaneous or transapical transcatheter valve repair and replacement systems that can be implanted without cardiopulmonary bypass often requiring only local anesthesia. Percutaneous transcatheter valve repair has especially become increasingly feasible, with a remarkable safety profile and a broadening clinical applications. While surgery remains the treatment of choice in *degenerative* MR, COAPT, and MITRA-FR have greatly enhanced our knowledge on intervention in *functional* MR. These data come as a relief after years of no clear direction timing of mitral valvular intervention and the role for percutaneous repair in patients with chronic severe *functional* MR. We also await results from the currently enrolling RESHAPE-HF2 randomized controlled trial to confirm or reject previously mentioned hypotheses on response to MitraClip treatment in severe functional MR. Results from COAPT will especially set the benchmark for future trials in the field of percutaneous mitral repair. Beyond the MitraClip, data comes from smaller experiences and there essentially is a crowding of percutaneous devices waiting to set themselves apart as more large-scale clinical trial data comes to light. We have embraced these new technologies and continue to witness expansion in minimally invasive transcatheter techniques with better safety and efficacy profiles over time that challenge current standards and greatly assist in caring for patients across several spectrums for surgical risk. Several of the MV percutaneous MV repair methods complement each other and may have longer-term durability and greater clinical impact. Evolutions in imaging technologies and fusion of 2D/3D echocardiographic with fluoroscopic imaging, allowing simultaneous viewing and superimposition of the different techniques, will further enhance safety, lower complication rates, shorten procedure times, accelerate achievement of technical expertise and optimize execution of these minimally invasive percutaneous procedures.

AUTHOR CONTRIBUTIONS

MS and UJ were involved in the planning, the writing of the manuscript, and making the figures and the tables.

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Transcatheter Mitral Valve Chordal Repair: Current Indications and Future Perspectives

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Transcatheter Mitral Valve Repair (TMVRe) technologies constitute a rapidly expanding field, and have the potential of being adopted as a valuable alternative to surgery in selected patients. TMVRe devices can be distinguished depending on the targeted part of the Mitral Valve (MV) apparatus. Standard classification includes leaflet repair, direct/indirect annuloplasty, chordal repair, and ventricular/chamber remodeling devices. We present the current device situation on chordal repair technologies. Nowadays, transapical off-pump beating heart chordal implantation procedure has become a safe and reproducible option for Degenerative Mitral Regurgitation (DMR). Besides the truly minimally-invasiveness of the procedure, another unique advantage offered by a beating-heart chordal implantation is the real-time assessment of chordal length adjustment during heart cycle with a normally filled left ventricle. Currently, one system is commercially available in Europe, the NeoChord DS 1000 (NeoChord, Inc., St. Louis Park, MN) and the Harpoon TDS-5 (Edwards Lifesciences, Irvine, CA) should become available soon. There is also a diffuse and strong interest to move from a transapical procedure toward a fully transcatheter (transfemoral and transeptal) procedure as shown by the increased number of preclinical programs under development. Interestingly, to achieve outcomes that equate to those of open surgery in DMR, transcatheter therapies will need to follow rigid indications due to strict patient selection criteria for each device, or adopt multiple techniques in a single repair procedure for complex MV disease. Continuous analysis of current clinical results together with future dedicated trial will be of extreme importance to foster the new and upcoming field of transcatheter MV therapy technology development.

Keywords: transcatheter mitral valve repair technologies, mitral regurgitation, transcatheter mitral chordal repair, transcatheter chordal implantation, transcatheter off-pump beating heart neochordae implantation

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INTRODUCTION

Mitral regurgitation (MR) is the most frequent valvular heart disease (VHD) requiring surgery in the United States and the second most common in Europe (1). Currently, surgical mitral valve repair (MVRe) and replacement (MVR) are the treatment options for the management of patients with mitral valve (MV) disease. American and European guidelines support surgical repair over replacement (2) because of the improved survival in degenerative MV disease. In case of functional MV diseases the recommendation is not clear because of presence of conflicting data.

In general, principles of MVRe include preservation or restoration of leaflet anatomy, creation of a large surface of leaflet coaptation and remodeling of the annulus to provide an optimal and stable orifice area.

In recent years, the classical leaflet resection techniques have been challenged by the introduction of more tissue-sparing approaches which include the implantation of artificial ePTFE chords to restore physiological leaflet behavior.

The next step in the progress cycle, which is currently underway, is to move from surgical on-pump procedure toward beating-heart transcatheter solutions (**Table 1**).

TMVRe devices can be distinguished based on the targeted component of the MV apparatus and classified into leaflet repair, annuloplasty, chordal repair, and ventricular/chamber remodeling. This classification can also include some overlap (3).

Transapical approaches have been recently introduced as well as new transfemoral devices currently in the developing phase.

NEOCHORD

The Neochord DS 1000 device (Neochord Inc., St. Louis Park, MN) has been the first transapical chordal implantation device available for clinical use in Europe (4–7). CE mark approval was gained in December 2012 following the results of the TACT trial (4). It is currently under investigation in US, where it is ongoing an IDE trial (RECHORD Trial), comparing surgical MVRe with NeoChord MV repair. An early clinical experience is also growing in Hong-Kong and China with a plan to extend its use to other Asia-Pacific countries in the next future. Currently more than 1,200 patients have been treated with this device.

The procedure is performed under general anesthesia, through a left mini-thoracotomy access in the fifth-intercostal space with 2D/3D real-time TEE guidance. The left ventricle (LV) entry site is identified about 2–4 cm postero-lateral from the real apex in order to obtain a perfect posterior and symmetrical alignment with the papillary muscles (8). LV navigation is performed using 2D X-plane views respecting the standardized step-by-step guide that consider the LV divided in two zones: "chordal free" and "chordal zone" (9). Once the MV plane is crossed, 3D transesophageal echocardiography becomes the leading imaging source. The target portion of the valve is identified, the device is opened and the leaflet is captured using the fiber optic monitor to confirm good leaflet grasp.

The leaflet is pierced and the ePTFE chord is passed through the leaflet and retrieved together with the device from the LV. A girth knot is performed allowing for leaflet fixation of the chord. The procedure is repeated for the total number of Neochordae intended to be implanted. Under 2D and 3D TEE control, all the chords are tensioned until adequate leaflet coaptation is achieved, and the neochordae are then secured to the LV wall using a large Teflon pledget (3) (**Figure 1**).

NeoChord procedural safety has been evaluated by single centers studies showing low mortality (1.4%, 2 extreme-risk patients considered inoperable for conventional surgery) and morbidity, good acute procedural success (98.6%) (10). Patient success (MR $\leq$ 2+ and freedom from reoperation) was 89% at 1 year (11). A recent multicenter European study, including 213 patients, confirmed high procedural success of 97.6% and good mid-term results with overall survival of 98 $\pm$ 1% and patient success of 84 $\pm$ 2.5% at 1-year follow-up (5).

More recently Seeburger and coauthors presented the 5 years results of the 6 patients enrolled at University of Leipzig in the TACT trial. Three patients were converted to surgery because of procedural failure and in another 3 patients residual MR at 5 years was significantly less than moderate and experiencing good clinical condition with no symptoms (12).

Based on the initial experience gained by early adopters the procedure underwent continuous technical refinement. LV access site was modified with a more postero-lateral access, echocardiographic views for navigation and grasping were standardized, tensioning was achieved with the use of tourniquets and epicardial stiff Teflon pledget. Moreover, patient selection criteria were refined combining echocardiographic measurement and morphology description.

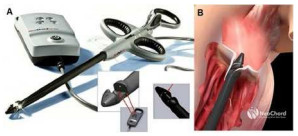
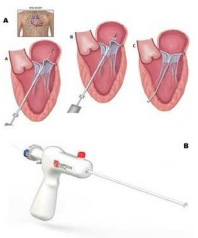
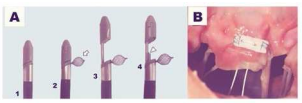
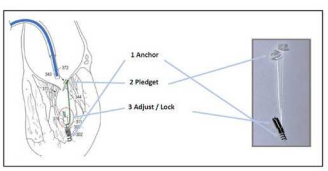
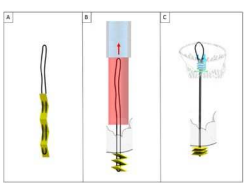
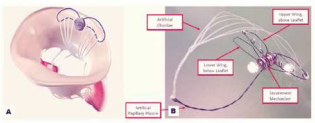
In particular MV morphology was characterized based on growing complexity as "Type A" isolated central posterior leaflet prolapse/flail, "Type B" posterior multi-segment prolapse/flail, "Type C" anterior or bi-leaflet prolapse/flail, "Type D" para-commissural prolapse/flail or any type of disease with presence of significant leaflet/annular calcifications. Outcomes are strictly connected with the morphological classification (8, 13).

The central echocardiographic selection criteria became the leaflet-to-annulus index (LAI) (14) that evaluate the leaflet to annulus mismatch. LAI is calculated as the ratio between the sum of anterior and posterior leaflet height and the antero-posterior diameter and represents the amount of overriding tissue that could generate the leaflet coaptation surface. The cut-off value of 1.2, corresponding to a 20% excess of leaflet tissue, is significantly related with an MR $\leq$ mild at 1 year follow-up. The LAI can be considered also as an expression of the leaflet-annulus mismatch. The NeoChord ringless procedure showed that annular dilatation should be considered not as an absolute concept but should be always considered in relation to the extension of the leaflets. If LAI is between 1.15 and 1.25 and in presence of isolated central prolapse/flail, a more anterior access site can be achieved in order to improve post-operative mid-term results. This slight modification changes posterior leaflet working angle, stretching it below the anterior leaflet consequently increasing final leaflet coaptation. However, interference with anterior subvalvular apparatus during ventricle navigation should be carefully considered in order to avoid native chordae damage (15).

Acute echocardiographic data analysis, demonstrated a significant reverse remodeling, both of the antero-posterior annular diameter and of the LV cavity volume;

Abbreviations: TMVRe, Transcatheter Mitral Valve Repair; MV, Mitral Valve; MR, Mitral Regurgitation; PML, Posterior Mitral Leaflet; LV, Left Ventricle; VHD, Valvular Heart Disease; DMR, Degenerative Mitral Regurgitation; MVRe, Mitral Valve Repair; MVRS, Mitral Valve Repair System; ePTFE, expanded Polytetrafluoroethylene; TEE, Transesophageal Echocardiography; LAI, Leaflet-to-Annulus Index; TA, Transapical; TF, Transfemoral.

TABLE 1 | Table of the present chordal repair technologies.

Device name	Mechanism	Trial status	Access	Figure
NeoChord DS 1000 (NeoChord Inc.)	Transapical off-pump beating heart neochordae implantation	CE mark approved	TA	
Harpoon TDS-5 (Edwards Lifescences)	Transapical off-pump beating heart neochordae implantation	Clinical trial completed, commercialization expected for Q1 2020	TA	
MitralStitch (Hangzhou DeJin Medtech Co)	Transapical off-pump beating heart neochordae implantation	Clinical Trial evaluation	TA	
ChordArt (Coremedic)	On pump beating heart Neochords sutureless implantation	Clinical Trial (Surgical) Preclinical (TF)	Surgical minithoracotomy (TF under development)	
Valtech V-Chordal Transfemoral (Valtech)	Trans-septal device for off-pump beating heart neochord implantation	Preclinical underway Clinical Trial (Surgical)	TF	
Pipeline	Trans-septal device for off-pump beating heart Neochord implantation	Preclinical underway	TF	
CardioMech (CardioMech, Oslo, Norway)	Trans-septal device for off-pump beating heart Neochord implantation	Concept	TF	
ChoRe (ChoRe, Delf, Netherlands)	Trans-septal device for off-pump beating heart Neochord implantation	*Ex-vivo* test	TF	
Mitral Butterfly (Angel Valve, Vienna)	Trans-septal device for off-pump beating heart Leaflet stabilization and Neochord implantation	Proof of Concept	TF	

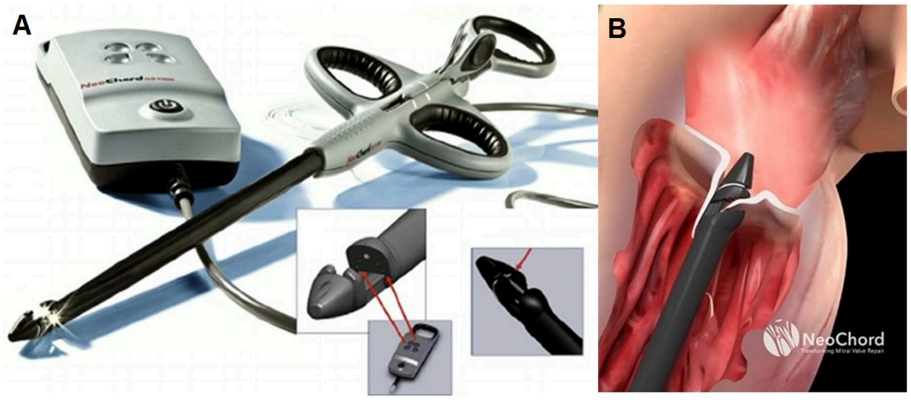


FIGURE 1 | (A) Shows the NeoChord DS 1000 system (NeoChord, Inc., St. Louis Park, MN), **(B)** exposes its application on mitral posterior leaflet through a trans-ventricular access.

these findings were maintained at 1 year follow-up damage (14).

The combination of procedure standardization, technical refinements, and understanding of selection criteria has been analyzed in a single center experience requiring almost 50 procedures as shown by the CUSUM analysis performed (16). Operators had to acquire new surgical skills as well as new visualization training passing from the usual direct surgical view to an echocardiographic real time guidance (17). Despite all these new factors the threshold beyond which the number of deaths or ineffective procedures would be unacceptable was never reached, showing a high safety and efficient profile of the procedure even in its early adoption phase. A recent analysis showed also that the majority of suboptimal results were due to technical factors occurring during the conduct of the operations. To reduce the learning curve effect associated with this procedure, a dedicated preclinical training program was introduced. The training is based on a proctored highly realistic procedural simulation using and *ex-vivo* pulsatile model that reproduces all the steps of the procedure with direct endoscopic and TEE control (18).

Recently, the company announced to be actively involved in the development of a transcatheter chordal repair and edge to edge programs.

In conclusion, Neochord repair procedure is currently considered a viable option for a subset of patients presenting with isolated, simple posterior leaflet lesion set.

HARPOON

Harpoon Mitral Valve Repair System (MVRS; Edwards Lifescences, Irvine, CA USA) is a sheeted 10 Fr device developed for transapical, beating-heart chord implantation. As for Neochord DS 1000, the procedure is performed under 2D and 3D transesophageal echocardiography guidance. Harpoon system allows the implantation of an ePTFE specially designed chord that is fixed on the MV leaflet by using a preformed double-helix coil knot.

Harpoon system is composed of a 14 Fr external diameter introducer with an inner hemostatic valve and a delivery system. The introducer sheet is inserted in the LV more anteriorly than in the Neochord procedure and fixed to the epicardial surface by using conventional "U-pledgets" purse strings. The delivery system contains a 21-gauge needle tightly wrapped with a pre-formed ePTFE bulky knot. When the tip of the delivery system is positioned under the target part of the diseased leaflet using 2D TEE guidance the knot is released by the penetration of the needle through the leaflet tissue. The needle is rapidly withdrawn and the ePTFE coil is tightened forming a double-helix on the atrial surface of the leaflet that secures the artificial chord (19) (**Figure 2**).

The system is then retrieved from the LV leaving outside the two ends of the ePTFE chord. The procedure can be repeated using a different delivery system for each implant. When the desired number of chords is reached, the introducer is removed and the pure-string sutures closed. Under 2D TEE guidance all the chords are tightened together to reach the desired final coaptation and then are secured to the epicardium with a large Teflon pledget as previously described (20).

Harpoon MVRS received CE mark approval in late 2017 but it is not yet commercially available. The TRACER trial (Mitral TransApical NeoCordal Echo-Guided Repair; prospective non-randomized multicenter clinical study) was conducted to test safety and efficacy of the device. Thirty patients were enrolled in 6 different European Centers. All patients presented severe degenerative MR due to isolated P2 disease. Patient population was highly selected based on presence of an adequate ratio between the posterior prolapse length and the corresponding antero-posterior distance between the free edge of the anterior leaflet and the base of the prolapsed posterior leaflet segment. The ratio should be greater than 1.5, meaning that the redundancy of the tissue should be extremely significant.

Six-month follow-up data were published (21), showing a good safety profile with no perioperative deaths and 20%

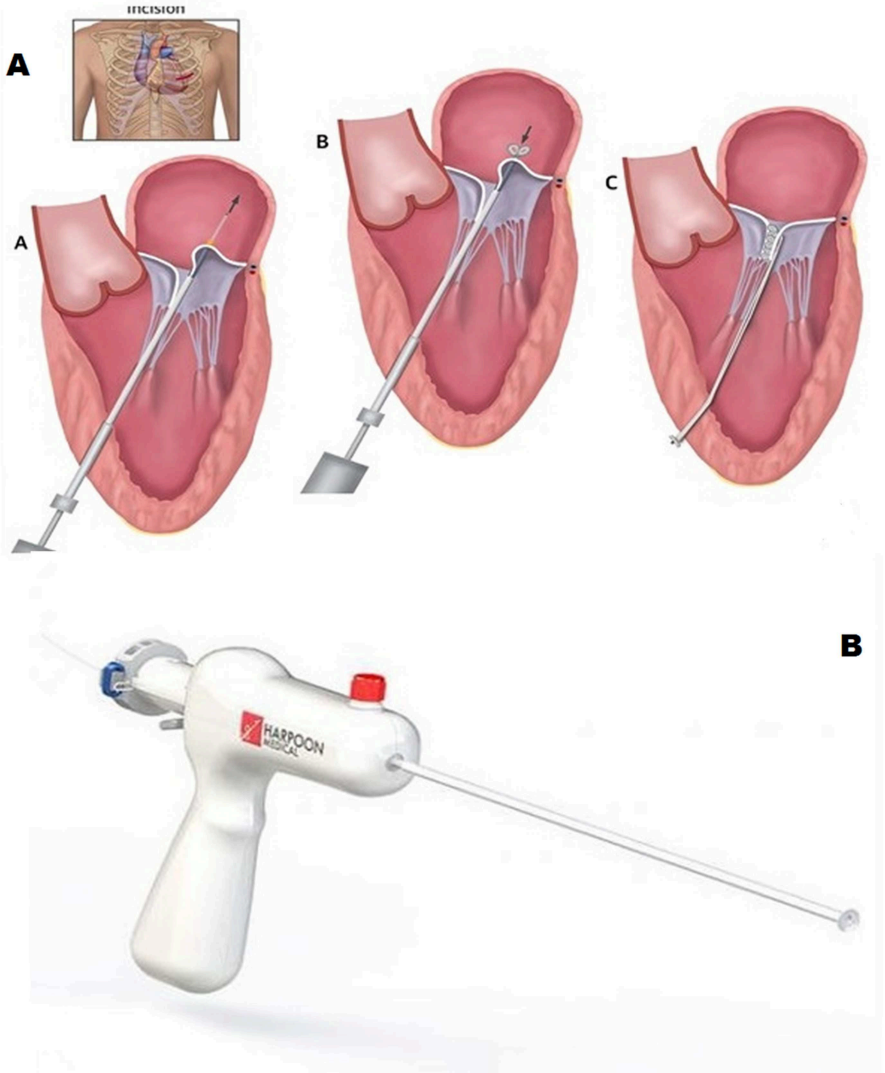


FIGURE 2 | (A,B) Show the surgical steps of the chordae implantation with the Harpoon device **(B)**.

SAEs rate within 30-days. Procedural success was 93% with two intraoperative conversions to open surgery. At 6-month follow-up, 76% of patients presented mild or less MR, 7% moderate MR, and 7% severe MR and 3 patients underwent conventional reoperation for severe MR recurrence. Moreover, the Harpoon procedure is likely associated to positive LV reverse remodeling with reduction of LV end-diastolic volume at 6-month and with reduction of MV antero-posterior diameter (19% reduction at 30 days, maintained up to 6-month follow-up). More recently, at the 2019 TVT Structural Heart Summit, investigators presented the last updated results of Harpoon one-year follow up clinical experience[1]. Sixty-five patients were enrolled and 62 were treated (1 aborted procedure, 2 converted to open surgery). At follow-up 10 patients exit from analysis because of death (2 cases) or secondary intervention for recurrence of MR (8 cases). With a mean follow-up of 1.4 $\pm$ 0.6 years. Of the 52 patients available for echocardiographic evaluation, half presented non/trace MR, 23% mild MR, 23% Moderate MR, and 2% severe MR. Analysis showed a stabilized cardiac revere remodeling observed at 30-postoperative days.

MITRALSTITCH

MitralStitch (Hangzhou DeJin Medtech Co Ltd., Hangzhou, China) is a transapical device for beating heart chordal implantation. A pledgeted ePTFE chord is implanted directly in the body of the leaflet avoiding direct suture loop or knots (22). A special feature of the device is the leaflet positioning system, made of a nitinol frame, specifically designed to be retrievable and to provide a precise grasping

[1]https://www.tctmd.com/slide/harpoon-transapical-technology-and-clinical-updates

of the leaflet (**Figure 3**). The procedure is performed under general anesthesia with echocardiographic guidance through an anterior mini-thoracotomy in the 5th intercostal space. Clinical experience has been evaluated in an early feasibility study that enrolled 10 patients showing 100% procedural success. Recently, investigators showed, as previously reported for the Neochord operation (23), that the same device could be used to perform and edge-to-edge repair implanting chords on both leaflets and by tightening them together with a locking device. A Chinese trial to access market is expected to start in summer 2019.

CHORDART

ChordArt (Coremedic, Biel, Switzerland) is a transcatheter mitral repair system. It consists of 3 components: a proximal nickel-titanium anchor for leaflet securement, a distal ventricular/papillary muscle anchor and the ePTFE chord. This special configuration has been proposed to be easily translated into a percutaneous transfemoral-transeptal delivery catheter. The device is currently under clinical evaluation using traditional surgical on pump approach (CHAGALL Trial, NCT03581656). The deployment procedure develops in a stepwise fashion. The leaflet is reached by an antegrade approach and grasped. The leaflet is punctured and the needle tip is passed through the leaflet till the papillary muscle where the first anchoring system is implanted. The needle is then retrieved and the leaflet anchor is released restoring normal leaflet coaptation (**Figure 4**).

Clinical data of the first surgically implanted device are not yet available.

V-CHORDAL

V-Chordal Adjustable Artificial Chordae System (Valtech, Or Yehuda, Israel), is a surgical transcatheter technology allowing on-pump chordal implant with off-pump beating heart length adjustment (24) (**Figure 5**). Through a left atrial roof incision, the device crosses the left atrium and the MV to reach the papillary muscles where an ePTFE chordal loop is placed. Once helical fixation element have been deployed on papillary muscle, the new chordae are then sutured to the mitral leaflet and atrium is closed leaving the device inside. After weaning from cardiopulmonary-bypass under TEE guidance the surgeon could perform beating heart chordal length adjustment.

Despite clinical-feasibility study has been completed on 6 patients, the transfemoral approach has not been further developed.

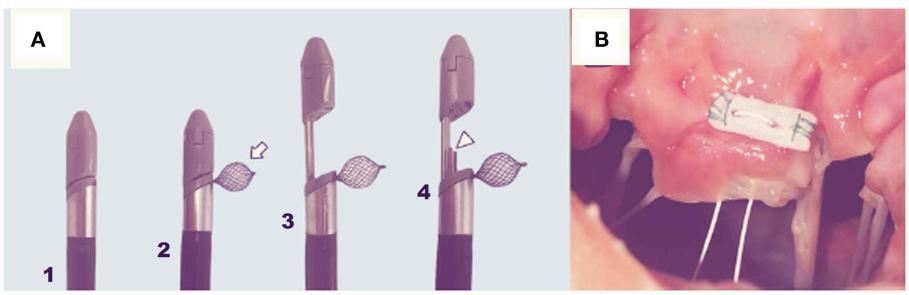


FIGURE 3 | The MitralStich grasping system with confirmation tool highlighted as well as with the nitinol positioner expanded **(A)**. The pledgeted suture deployed on the targeted leaflet **(B)**.

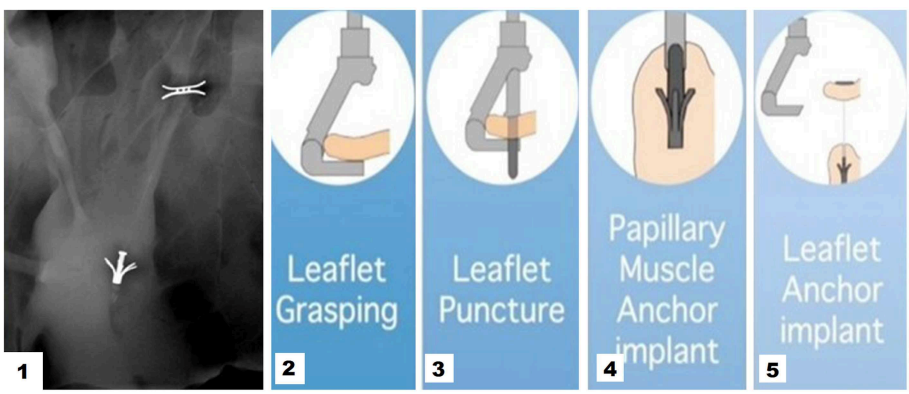


FIGURE 4 | 1 Cardiac fluoroscopy showing final ChordArt implantation. 2–5 Implantation steps of the device.

PIPELINE

Pipeline (Gore Medical, USA) is a transcatheter device designed for off-pump, beating heart chordal replacement. As seen for other devices, transfemoral-transseptal way is used to access the left atrium and drive a guidewire across the MV inside the LV.

Once driven on the site, Pipeline is advanced up to the papillary muscles. First, a distal ventricular/papillary muscle helical anchor is deployed. The leaflet is than punctured and the leaflet fixation system is folded up by pulling the artificial Neochord forming this way tissue anchoring. The artificial Neochordae results connected at one side to the ventricle wall by means of the distal anchor and at the other side to the leaflet through the auto-deploying system. The third step consists in suture length adjustment and locking. Under 2D/3D TEE guidance a suture lock device is delivered inside the LV. The chord is then tensioned in order to reach the best coaptation and consequent MR reduction. The residual part of the suture is then cut, disconnecting the device from the LV anchor (**Figure 6**). The device is under preclinical animal testing.

CARDIOMECH

CardioMech (Trondheim, Norway) is developing a percutaneous solution for artificial chords implantation. Currently there are no available information about phase of development of the project. The Company website describes a length adjustment device delivered via transvenous-transeptal approach. It comprises a gripper element housing a self-expandable folded anchor made of memory shape material. When the leaflet is grasped, the anchor is unfolded and is secured to the leaflet by piercing it.

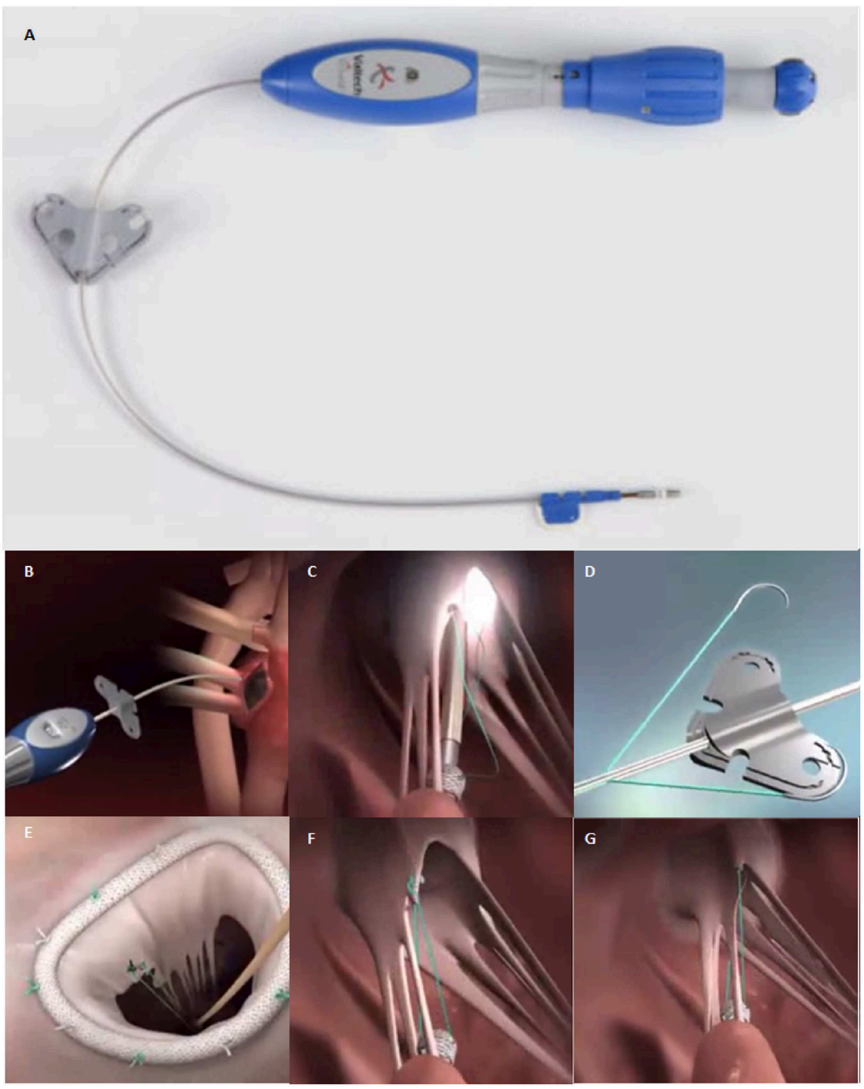


FIGURE 5 | (A) The V-Chordal device. **(B)** Crossing of the left atrium and the MV. **(C)** Deployment of the helical fixation anchor on the papillary muscle. **(D)** ePTFE chordal loop is released. **(E)** The new chordae are then sutured to the mitral leaflet. **(F,G)** Final result after chordal length adjustment.

The catheter device also holds a self-expandable folded papillary anchor made by shape memory metal. The chord extends from the leaflet anchor to the papillary anchor. The chord length is adjustable under real-time echocardiographic guidance. Interestingly the excess of chord length in the atrium is then cut and all catheters are withdrawn (**Figure 7**).

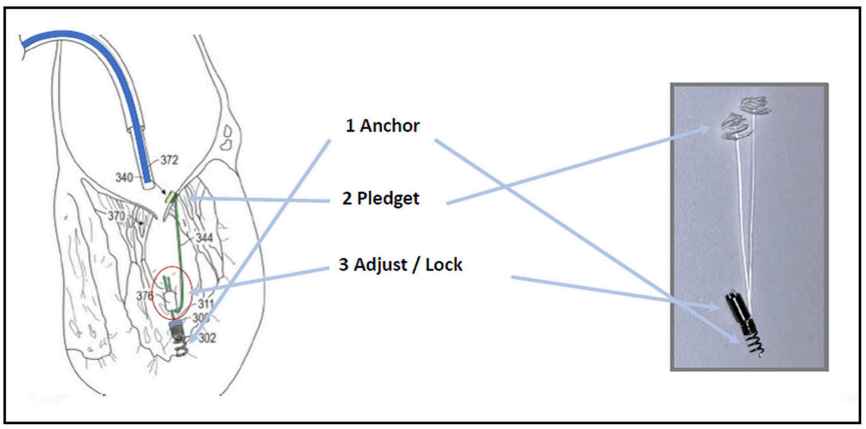


FIGURE 6 | The Pipeline Device.

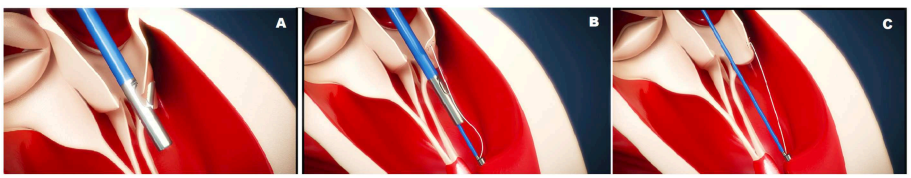


FIGURE 7 | The CardioMech implantation procedure steps. **(A)** PML is grasped and punctured. **(B)** The artificial chord is anchored to the papillary muscle. **(C)** The chord is tensioned.

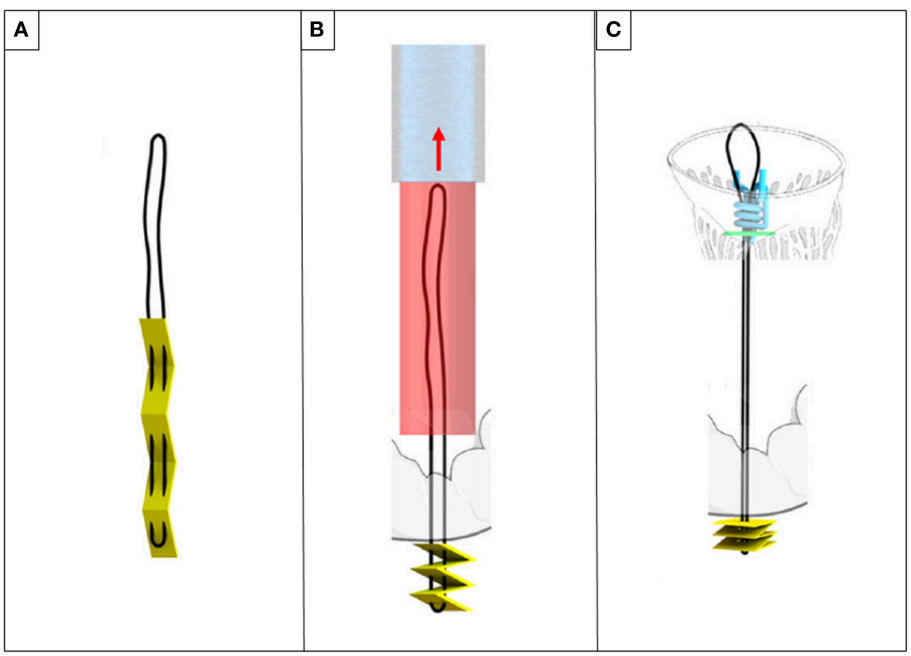


FIGURE 8 | ChoRe **(A)** the artificial chord with the apex pledget. **(B)** The apex pledget folds into an accordion shape, by backword movement of the device and interaction with the ventricle wall. **(C)** The pre-constructed knot is tightened around the chord to provide the correct length and a secure fixation to the atrial wall of the leaflet.

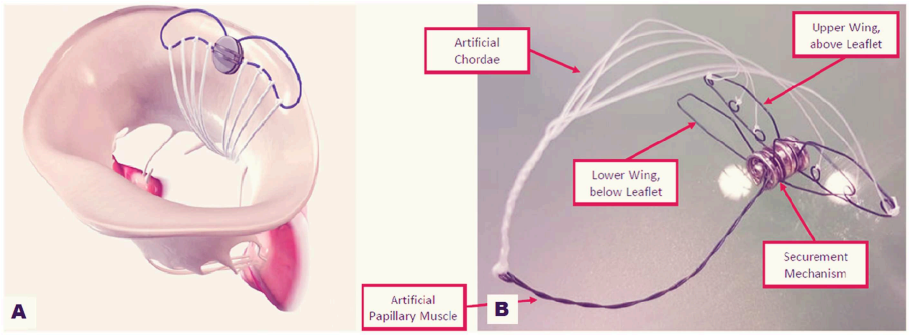


FIGURE 9 | Mitral Butterfly device: **(A)** implanted on the posterior annulus and leaflet. **(B)** The device in its components.

CHORE

The ChoRe is an underdevelopment device for transfemoral implantation of chords with an epicardial fixation. The procedure steps can be divided in apex fixation, leaflet fixation, and a length adjustment. In the first step of the procedure, a needle puncture the ventricular wall providing externalization of the chords on the epicardium surface together with a folded pledget (**Figures 8A,B**). In the second step, the device is retrieved toward the mitral valve. Leaflet grasping is performed a needle passes through the leaflet and hooks the implanted chord. The leaflet fixation is achieved with implantation of a pledget. Finally, during the third step, a pre-constructed knot (**Figure 8C**) is fastened and left on the atrial PML surface.

The system has been recently presented as a concept and *ex-vivo* tests have been performed. A scaled-up size prototype (twice as large as the final device size) has been tested *ex vivo* in bovine hearts (25).

The test showed a good performance of the prototype. Ten artificial chords have been successfully implanted, with an average time of 3.45 ± 1.44 min.

However, the authors disclosed the need for improvement in the apex fixation, leaflet fixation and chordal adjustment phase. In case of apex connection, concerns about bleeding must be considered. Moreover, the length of artificial chords is longer respect to papillary muscle fixation procedures, leading to worse mechanical proprieties of the implant. Finally, the pre-constructed knot seemed not to be able to firmly maintain the point of anchorage when pulled. Future work will focus on improvement of these matters.

MITRAL BUTTERFLY CHORDAL MESH REPAIR

Mitral Butterfly (Angel Valve, Vienna Austria) is a concept technology that can hold and capture the entire prolapsing MV leaflet segment restoring its normal geometry (**Figure 9**) The device is delivered through a transeptal or transaortic approach and is made of a nitinol-stent with ePTFE yarns which act as artificial chordae. When deployed, the shape memory stent unfolds, holding the prolapsing leaflet segment. The ePTFE yarns replace broken chordae, preventing prolapse/flail. A hook extends in the ventricle, mimicking a papillary muscle, and is coupled with the ePTFE filaments. Thanks to its characteristic design, the mitral annulus remains untouched and no unintentional forces strain the myocardium. Proof of concept was verified using passively perfused porcine hearts. *In vivo* preclinical tests have been planned for 2019.

CONCLUSION

The wide variability of MV morphologies drives continuous development of technologies to treat the full spectrum of MR pathophysiology. Consequently a variety of transcatheter MV devices for the percutaneous treatment of MR have been developed. The chordal device spectrum is composed of a big player with a solid clinical experience and many new devices that will enter into clinical practice soon as well as new early phase devices that are still under development. Many companies are working on percutaneous solutions in order to minimize invasiveness as well as to create a more physiological fixation at the level of the papillary muscle or in the base of the LV in between the papillary muscles.

Careful patient selection remains the basic step foregoing any TMVRe technology, and this concept could be even more relevant considering the Chordal Repair therapy. Because of the multifaceted presentation of MV disease, traditional surgical procedures have always combined different leaflet and annular therapies. The current solid surgical background will stimulate the already presented MV transcatheter repair tool-box concept (26, 27) for complementary use of different devices to perform a surgical-like transcatheter MV repair. Moreover, the appropriate combination of leaflet, chordal, ventricular devices together with annular devices and the concomitant innovation in imaging and catheter development will progressively improve long-term outcomes, allowing a future extension of these technology indications to lower-risk patients and the adoption of them as a first-line treatment strategy. However, we must consider that despite early positive results, that

are better than those of the early Mitraclip experience and better than what was predicted by the traditional surgical community, long-term durability and effectiveness remain to be proven for all transcatheter chordal devices.

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frontiers in Cardiovascular Medicine

MINI REVIEW
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Percutaneous Mitral Edge-to-Edge Repair: State of the Art and a Glimpse to the Future

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Patients with severe symptomatic mitral regurgitation have a poor prognosis if left untreated. In those patients who are not eligible for mitral valve surgery, percutaneous edge-to-edge repair may improve clinical outcomes. Recent clinical trials have added to our knowledge and provide interesting insights into the management of such patients. With an increasingly aging global population, these technologies are likely to represent an important treatment option. This mini-review will examine the technology, the evidence and the latest developments in percutaneous mitral edge-to-edge repair.

Keywords: percutaneous mitral repair, mitral valve, mitral regurgitation (MR), MitraClip (MC), transcatheter mitral valve (MV) repair

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INTRODUCTION

It has been estimated that nearly 50% of patients with severe symptomatic mitral regurgitation (MR) are not referred for surgery, mainly because of age, and reduced left ventricular function resulting in high surgical risk (1). Conversely, 62% of patients with ischaemic secondary MR and systolic heart failure are dead within 5 years (2). In this light, the MitraClip (MC) mitral valve repair system (Abbott Vascular, Abbott Park, Illinois, USA) has taken center stage as a treatment option, particularly in the context of an aging population. The obvious advantages of a percutaneous approach are reduced invasiveness and rapid recovery. The first procedure was performed in 2003, CE mark obtained in 2008 and FDA approval for the treatment of primary MR in 2013. Transcatheter mitral valve (MV) repair compared with conventional MV surgery has demonstrated similar 5-year mortality in the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) albeit at the cost of treatment efficacy compared to surgical MV repair or replacement in patients with predominantly primary MR (3). Surgical treatment of secondary MR is not well established, therefore the recently published results of the randomized MITRA-FR and COAPT trials examining the additive benefits of MC on top of medical therapy specifically in secondary MR populations were highly anticipated (4, 5). While COAPT showed a 47% relative risk reduction of the primary endpoint (all hospitalizations for heart failure at 24 months), as well as a lower mortality after 2 years of follow-up (29.1 vs. 46.1%; hazard ratio, 0.62; 95% CI, 0.46–0.82; $p < 0.001$), no significant difference between groups were found in the smaller MITRA-FR study. These diametrically opposing results can be explained by diverging patient characteristics. This mini-review will examine the technology, the evidence and the latest developments in the field.

SURGICAL TREATMENT

Current European guidelines advocate surgical treatment for symptomatic severe primary MR as a class I indication. Surgery is also recommended in asymptomatic MR in the presence of predictors of worse outcome (atrial fibrillation, left ventricular ejection fraction ≤60%, or LVESD ≥45 mm or systolic pulmonary pressure ≥50 mmHg) or if there is a low surgical risk and a high chance of durable repair in patients with a LVESD ≥40 mm and either a flail leaflet or an enlarged left atrium (6). Although no randomized data are available, surgical repair is preferred over replacement where anatomically possible and is associated with a low recurrence in primary MR (90% of surviving patients after 20 years remain free of severe MR). Observational studies suggest improved clinical outcomes compared with MV replacement (7, 8).

In contrast, surgical repair of secondary MR has less favorable outcomes with increased perioperative mortality and MR recurrence rates as high as 60% within 2 years (9). In patients undergoing mitral-valve repair or replacement for severe ischemic mitral regurgitation, no significant between-group difference in left ventricular reverse remodeling or survival was seen at 2 years. Mitral regurgitation recurred more frequently in the repair group, resulting in more heart-failure–related adverse events and cardiovascular admissions. However, reverse remodeling at 2 years was observed after successful repair rather than replacement (10).

The Alfieri surgical edge to edge repair operation was designed to reduce MR by creating a double orifice from the placement of a stitch joining the free edge of the anterior and posterior mitral valve leaflets (11). The benefit of the operation was effective reduction of MR using a relatively easy and reproducible technique, although it is often combined with annuloplasty for a more durable result.

Despite surgical treatments being available, it is estimated nearly 50% of patients with severe MR are not referred due to prohibitively high risk as a result of age and comorbidity (12). In those older and more comorbid patients undergoing surgical treatments for MR there is generally no increase in long-term survivability and uncertain benefit on quality of life (13). A less invasive treatment option would therefore be particularly appealing for this patient group.

PERCUTANEOUS MITRAL LEAFLET REPAIR

The success of transcatheter aortic valve replacement has demonstrated the benefits of innovation in the domain of the treatment of structural heart disease. As this field grows, the next frontiers are effective interventional treatments for the mitral and tricuspid valves. The only percutaneous leaflet repair system with both FDA and CE mark approval is the MitraClip (Abbott, Abbott Park, Illinois). Its competitor, the PASCAL System (Edwards Life sciences, Irvine, California), recently obtained CE mark and a pivotal trial is currently underway aiming for FDA approval. Both systems aim to approximate the mitral valve leaflets to reduce MR.

PRE-PROCEDURAL PLANNING

Pre-procedural planning for MC includes a comprehensive echocardiographic assessment for a precise depiction of the underlying mechanism for regurgitation, as well as grading of MR severity.

On transthoracic echocardiography (TTE), biventricular size and systolic function, left atrium size, other significant valvular disease and estimation of pulmonary pressure based on the Guideline recommended imaging windows and parameters should be obtained (14).

Transesophageal echocardiography (TEE) is the mainstay for MR intervention screening because of its key role in intraprocedural guidance. A careful examination of the mechanism of MR and quantitative assessment of MR degree of severity should be reported. In addition to the standard 2D echocardiographic views, utilization of advanced imaging is particularly helpful to determine the presence of anatomic abnormality. The use of multiplane imaging allows a systematic visualization of all MV scallops, from the medial to lateral aspects of the MV (**Figure 1**). An en-face view of the atrial side of the entire MV (surgeon's view) and adjacent structures is possible using 3D imaging. Flail and prolapse segments, the location of clefts, deep indentations, perforations and significant malcoaptation gaps may be more apparent and easier to visualize. In addition, MV area can more precisely be measured (**Figure 2**).

Current European Guidelines recommend a multiparametric approach for the diagnosis of severe MR including semi-quantitative parameters (vena contracta ≥7 mm, systolic flow reversal in the pulmonary veins, mitral inflow dominant E-wave ≥1.5 m/s, and MR velocity (CW Doppler) TVI mitral/TVI aortic >1.4) and quantitative parameters (effective regurgitant orifice area (EROA) and the regurgitant volume (R Vol), which is ≥ 40 mm^2 and ≥ 60 ml for primary MR. In secondary MR, an EROA ≥ 20 mm^2 and R Vol ≥ 30 ml have been shown to have a prognostic value and therefore proposed to indicate severe disease in the European Guidelines, but not in the corresponding Guidelines of the American Society of Echocardiography (2, 6, 15). Quantification of MR severity should be performed using 2D or 3D proximal isovelocity surface area (PISA) method or preferably 3D vena contracta area.

Both TTE and TEE should be reviewed by the Heart Team to confirm eligibility and intraprocedural approach to MV repair. Agreement should be made as to the precise location for device placement, number of device, and treatment strategies, particularly with more challenging anatomy as defined in **Table 1**.

ABBOTT MITRACLIP: THE PROCEDURE

The MitraClip device has been implanted in over 100,000 patients worldwide. It is introduced percutaneously via a 24 French orientable guiding catheter from the femoral vein using a

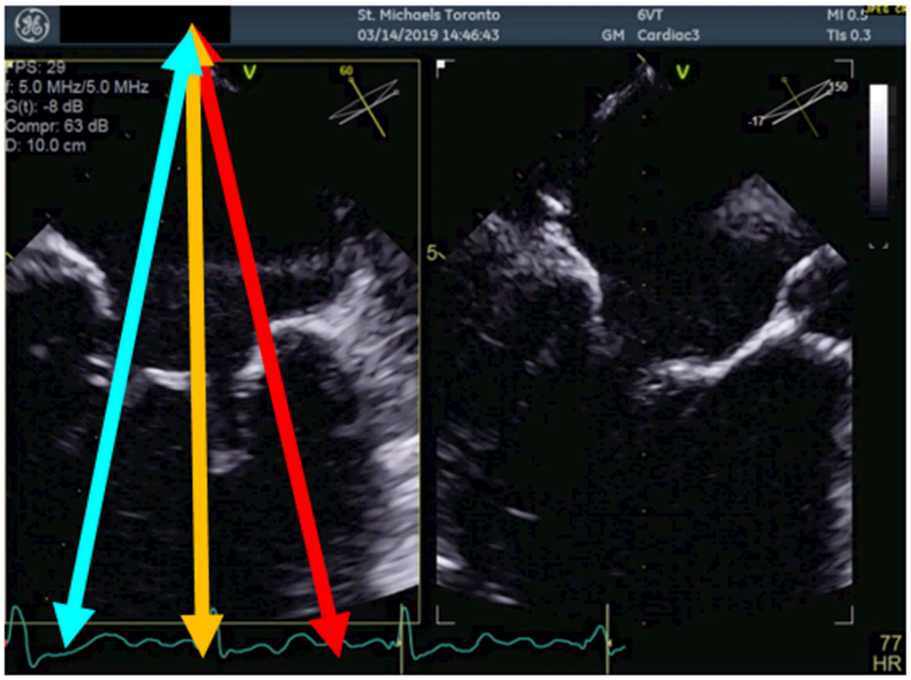

FIGURE 1 | Multiplane view of the mitral valve. Mid-esophageal biplane views (left panel: 60 degree view, right panel: 150 degree view) of the mitral valve leaflets. The blue arrow demonstrates the medial aspect of the mitral valve, the orange arrow, the central aspect and the red arrow, the lateral aspect of the mitral valve.

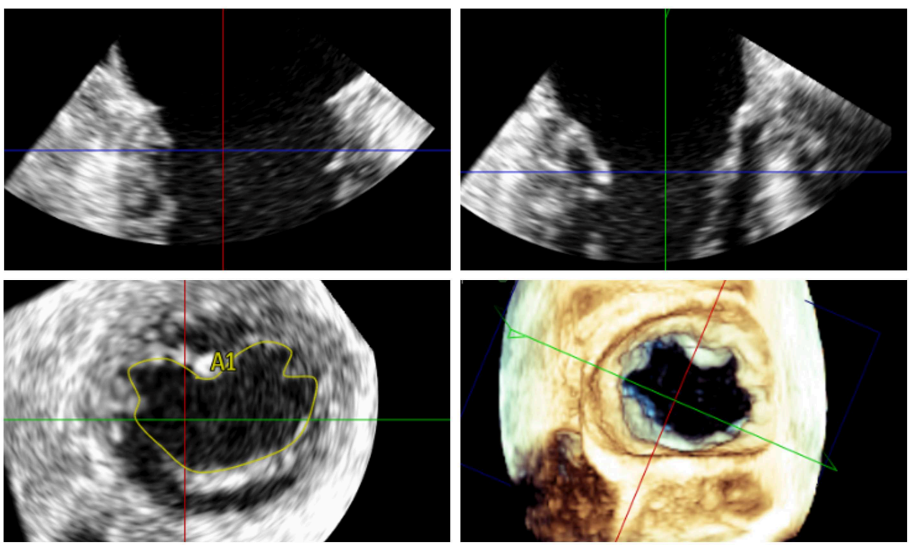

FIGURE 2 | Measurement of the 3D mitral valve area (MVA) by transoesophageal echocardiography in a patient with severe MR; the MVA in this case was 5.48 cm^2 indicating suitability for percutaneous mitral valve repair.

superior and posterior trans-septal puncture to access the left atrium. A steerable clip delivery catheter enables orientation of the clip whilst real-time 3D transoesophageal echo allows precision targeting of the free edges of the opposing leaflets at the site of regurgitation. The device is then advanced into the left ventricle and while pulling back the catheter, the mitral valve leaflets are grasped. Once optimal grasping has been undertaken, the clip is closed creating a double orifice. Transoesophageal echo is used to assess for adequate leaflet insertion, residual MR and new trans-valvular gradients avoiding mitral stenosis prior to final deployment. Direct measurement of LA mean pressure and V wave provides complementary hemodynamic data to guide

TABLE 1 | Anatomical considerations for percutaneous mitral leaflet repair.

Favorable	Unfavorable/contraindicated
Moderate-severe or severe MR	Commissural lesions
A2-P2 defect	Clefts
Prolapse width <15 mm	Short posterior leaflet (<5 mm)
Flail gap <10 mm	Mitral valve orifice area < 3.5 cm^2
Mitral valve orifice area > 4 cm^2	Severe calcification of grasping zone
Mobile length of the posterior leaflet ≥ 7 mm	Leaflet perforations
	Mitral stenosis with mean gradient ≥5 mmHg at baseline
	Active endocarditis or rheumatic heart disease

treatment decision-making. Multiple clips can be implanted to optimize imperfect results on a case by case basis if gradients and anatomy allow. Hemodynamics usually remain very stable during the procedure and recovery time is short.

NEWEST ITERATION: MITRACLIP XTR

There is currently a new version of the clip, the MitraClip XTR (MC XTR), which is similar to the first generation and NT versions of the MC in that it consists of a 24 French steerable guide catheter and a steerable clip delivery system (CDS). The MC XTR has a 5 mm longer clip grasping width due to longer arms (22 vs. 17 mm compared with the NTR). The transition zone between the delivery sheath and the CDS has been reinforced to improve stability during rotation of the CDS. The steerable sleeve is also more responsive to the rotation of the M-knob. The working length of the system has been increased by 1.5 cm and changes to the mechanism and material of the lock line enable operation of the system in the "unlocked" position. Finally a new Nitinol rather than Elgiloy gripper line enables a deeper gripper drop and grasping angle. Ultimately, the MC XTR may enable easier and quicker leaflet grasping, reduce the number of clips required and expand percutaneous treatment to patients with less favorable anatomy.

On the other hand, grasping more tissue may result in additional tension on the leaflets that concentrates at the tip of the clip arms. This may provoke leaflet damage, especially in patients with calcifications, fragile, or thin appearing leaflets. Moreover, due to the increased length of the clip arms, the risk of entrapment in the subvalvular apparatus is certainly higher, particularly when treating commissural lesions. According to a recently published multicenter experience in 107 patients treated with the MC XTR, procedural success was high with MR≤2+ in 93% of the patients and ≤1+ in 77%. However, four patients had leaflet damage requiring surgical correction during the same hospitalization (16). Thus, the use of the XTR system should be evaluated based on individual anatomy, rather than as a default strategy. Although requiring further evaluation, the combination of different clip sizes may represent a valuable treatment option in patients on whom valve area/gradient is borderline (**Figure 3**). It is anticipated that future iterations of the MitraClip will allow independent leaflet grasping.

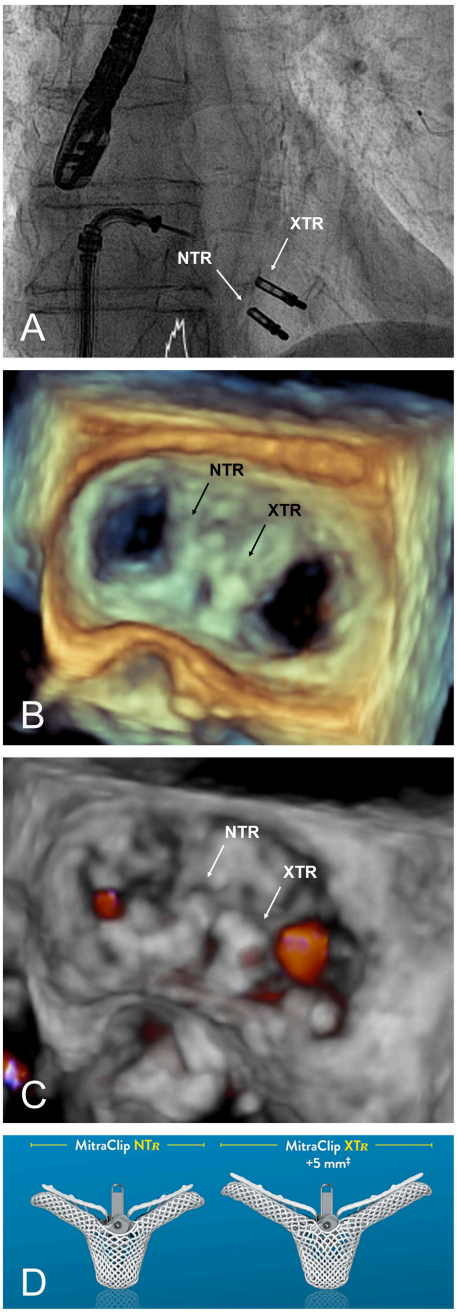

FIGURE 3 | (A) Fluoroscopic appearance of a successfully implanted XTR and NTR clip. **(B,C)** 3D transoesophageal echocardiographic view and Doppler, respectively, providing an en face view of the valve from the same case after implantation. **(D)** MitraClip versions currently available.

THE EDWARDS PASCAL MITRAL REPAIR SYSTEM (EDWARDS LIFESCIENCES, IRVINE, CA, USA)

The Edwards PASCAL Transcatheter Valve Repair System has been designed to address some of the limitations of previous systems. It is intended to reduce the tension on the valve

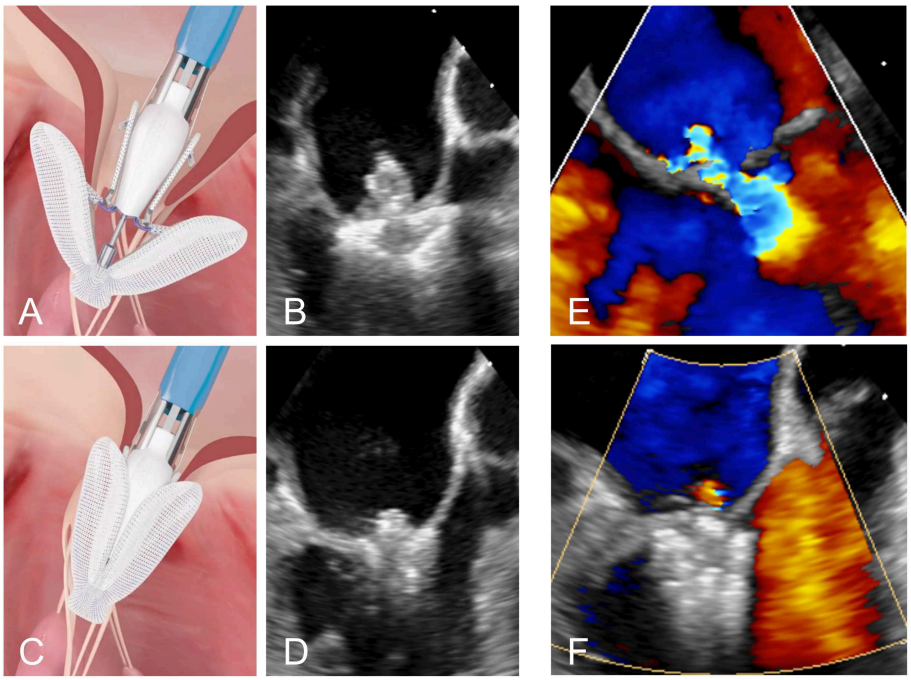

FIGURE 4 | (A,B) Positioning of the PASCAL device in the mitral valve. **(C,D)** Grasping of the two leaflets. **(E,F)** Transoesophageal Doppler image of a case of severe MR before and after leaflet repair with the PASCAL device, respectively.

leaflets by introducing a 10 mm central spacer within the MV regurgitant orifice. The paddles of the implant are also wider and curved to further reduce tension and the system allows for independent grasping of the leaflets. This may be particularly useful in the presence of a large prolapse gap (**Figure 4**) or in patients with retraction or tethering of the posterior leaflet. The device is also designed to be easier navigated in the left atrium and offers a higher degree of steerability. A first-in-human feasibility experience of the device has been described from a series of 23 compassionate use cases (17). These early data were encouraging with MR $\leq$2+ in 97% of the patients at discharge and without elevated gradients despite a larger device size.

The CLASP study is a multicenter, prospective trial of the PASCAL system in 62 patients with significant MR despite medical therapy, with independent adjudication of clinical events and central echo core lab. Mean age was 76.5 years, NYHA class II/IV in 51.6%, with 56% FMR, 36% DMR, and 8% mixed MR etiology. At 30 days, the major adverse event rate was 6.5%, with all-cause mortality of 1.6% (18). Overall, 98% of patients had MR $\leq$ 2+, and 86% had MR $\leq$ 1+, with 85% in NYHA Class I/II; significant improvements were also observed in 6 min walk distance and KCCQ scores. Based on these promising results, the PASCAL system gained CE mark in early 2019. The pivotal CLASP IID/F randomized trial has begun enrolment, and will compare the efficacy and safety of PASCAL vs. MitraClip in patients with significant DMR or FMR, using a non-inferiority study design.

EVIDENCE FROM RANDOMIZED TRIALS

EVEREST II (NCT00209274, Endovascular Valve Edge-to-Edge REpair Study) was the first randomized trial to examine the MitraClip system in 279 patients with moderate-to-severe or severe MR, comparing percutaneous therapy to conventional surgery in a respective 2:1 ratio (19). Published in 2011, this was a very early experience with the system for many of the recruiting sites. The percutaneous intervention arm demonstrated superior safety with similar improvements in clinical outcomes although was less effective at reducing MR compared to surgery at 1 year. The primary end point for efficacy (freedom from death, MV surgery, reintervention, and moderate-to-severe MR) was 55% in the MitraClip group and 73% in the surgical group at 12 months ($p = 0.007$). Major adverse events occurred in 15% of patients in the MitraClip group and 48% of patients in the surgical group at 30 days ($p < 0.001$). The 5 year follow-up from this study found the composite endpoint in the as-treated population was 44.2 vs. 64.3% in the percutaneous repair and surgical groups, respectively ($p = 0.01$) driven primarily by more MR and more subsequent mitral surgery in the percutaneous arm. Rates of surgery and moderate-to-severe MR were comparable between groups beyond 6 months, affirming the durability of both techniques. Notably, only 27% of the patients in this trial had secondary MR.

The French MITRA-FR study randomized 307 patients with symptomatic left ventricular dysfunction and significant

secondary MR to either medical therapy or medical therapy combined with the MitraClip procedure (5). 92% of patients achieved an MR grade ≤2+ immediately after the procedure while there was no difference in the primary outcome of all-cause death and unplanned re-hospitalization for heart failure at 1 year which occurred in 55% of the intervention group and 51% of the control group (odds ratio [OR], 1.16; 95% confidence interval [CI] 0.73–1.84; $p = 0.53$). The mortality rate was 24.3% in the intervention group vs. 22.4% in the control group (hazard ratio [HR], 1.11; 95% CI 0.69–1.77) at 12 months. As an important limitation, it has to be mentioned that a significant amount of follow-up data on echocardiographic outcome and functional status at 12 months were missing.

The presentation of the results from MITRA-FR were closely followed by the North American COAPT trial which randomized 614 patients with symptomatic heart failure and moderate-to-severe or severe secondary MR to medical therapy or medical therapy and MitraClip repair (4). The primary outcome was the rate of hospitalization for heart failure within 24 months which was 35.8% per patient-year in the device group as compared with 67.9% in the control group (HR, 0.53; 95% CI, 0.40–0.70; $p < 0.001$). Moreover, the powered secondary end point of death from any cause within 24 months was significantly lower occurring in 29.1% of the patients in the device group as compared with 46.1% in the control group (HR, 0.62; 95% CI, 0.46–0.82; $p < 0.001$). The number of patients needed to treat to prevent 1 hospitalization was 3 and to prevent 1 death was 6. All prespecified secondary endpoints including quality of life and functional assessments were significantly improved in the MitraClip arm.

While both trials examining MC in the context of secondary MR produced different results, there were major differences between the two trials. Firstly, due to differing definitions of severe functional mitral regurgitation between European and North American guidelines, mitral regurgitation was more severe in the COAPT trial than in the MITRA-FR trial (mean EROA of 41 vs. 31 mm^2). In addition, the indexed left ventricular end-diastolic volumes were smaller in COAPT as compared with MITRA-FR (101 ± 34 vs. 135 ± 35 ml/m2). Another difference between the trials may have been increased aggressiveness of the guideline directed medical therapy delivered to the patients in COAPT which was overseen by the screening committee. Taken together, this might mean the patients in COAPT had worse MR with relatively more preserved left ventricles representing a group a patients that benefit most from percutaneous edge-to-edge repair.

Secondly the number of patients receiving more than one clip was higher in COAPT possibly explaining the higher proportion of moderate-to-severe or severe residual MR at 1 year in MITRA-FR (17 vs. 5% in COAPT).

FUTURE DIRECTIONS

There are a number of questions still remaining with regards to percutaneous leaflet repair:

1. Empirical use of antiplatelet therapy for stroke prevention after the procedure has been advocated without any trial evidence. Recent registry data suggests the use of a NOAC with a single antiplatelet may prove beneficial as compared with antiplatelet therapy alone, especially in the first year post implantation (20). Randomized data would be needed to more accurately define the answer to this important question.
2. The evaluation of percutaneous edge-to-edge repair in cases of cardiogenic shock resulting from acute MR would be an interesting avenue to explore, particularly in the setting of subacute myocardial infarction where surgical repair remains hazardous.
3. The objective echocardiographic grading of post-procedural residual MR is very challenging and requires further validation.
4. The management of the atrial septal defect created during MitraClip has to be further clarified.
5. Continuous left atrial pressure monitoring is a promising but still not well-standardized method to evaluate outcome of repair.
6. Further data is required to understand what is the place of the PASCAL device within treatment options and whether it can tackle complex anatomy such as larger flail segments, shorter posterior leaflets, or cases involving mitral annular calcification; this may be answered by a future head to head trial.

The development of newer devices and iterations in the field of percutaneous leaflet repair may expand the spectrum of anatomies that can be treated. Patients with primary MR and favorable anatomy who are inoperable or at high risk for surgery, can reasonably be offered percutaneous mitral valve repair. In secondary MR, patient selection seems to be of paramount importance to optimize individual outcomes. Volume overload from excessive secondary MR should no longer be thought of as an innocent bystander but rather a contributing factor to poor outcomes in patients with heart failure. Based on the data available, guideline directed medical therapy for heart failure should be optimized with cardiac resynchronization where appropriate prior to consideration of percutaneous mitral valve repair. If despite these measures symptomatic moderate-severe or severe functional MR remains, an early approach to treatment should be considered before further deterioration of ventricular performance occurs. The early detection and appropriate management of these patients in a multidisciplinary Heart Team is crucial to allow timely interventional treatment. Identification of factors predicting response to the therapy is expected to be a topic of future research. Potential meaningful parameters may include the proportionality of MR related to ventricular dilation, the presence of myocardial fibrosis precluding ventricular remodeling, as well as the use of strain echocardiography to better appreciate myocardial function (21).

While new device iterations allow novel features such as independent grasping or increasing arm dimensions, they also introduce new challenges such as possible asymmetric grasping resulting in residual MR or excessive leaflet tension and thus require a further learning curve for optimal use.

With the recent advances in technology and an expanding knowledge base from carefully conducted randomized clinical trials, we are already glimpsing into a future where percutaneous therapies have an important role in the management of mitral valve disease and heart failure.

AUTHOR CONTRIBUTIONS

FK, MW, GO, FP, and NF: drafting of the manuscript and figures. NB: figures and critical revision of the content. SW and TP: critical revision of the content.

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REVIEW
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Percutaneous Mitral Valve Repair: Multi-Modality Cardiac Imaging for Patient Selection and Intra-Procedural Guidance

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Percutaneous mitral valve repair is an important procedure for patients at high risk of surgical mitral valve repair. Multi-modality Cardiac Imaging plays a key role in these procedures. MitraClip is the first and most utilized percutaneous mitral repair device and experience is has grown to treat not only typical but atypical and complex lesions. Cardioband is an emerging percutaneous annuloplasty system with promising early results. This review will focus on the comprehensive multi-modality cardiac imaging for patient selection and intra-procedural guidance of the MitraClip and Cardioband systems.

Keywords: mitral regurgitation, percutaneous mitral annuloplasty, percutaneous edge-to-edge leaflet repair, multimodality cardiac imaging, interventional echocardiography

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INTRODUCTION

Mitral regurgitation (MR) is one of the most common valvular diseases in the world. Percutaneous technologies have been increasingly investigated as an alternative to open heart surgery in high-surgical risk patients. Several mitral repair systems have been approved in the United States or Europe. The Mitraclip (Abbott Structural, Santa Clara, California) percutaneous edge-to-edge repair device has received Conformité Européenne (CE) mark approval for degenerative and functional MR in Europe as well as Food and Drug Administration (FDA) approval for degenerative and more recently functional MR in the United States. Cardioband (Edwards Lifesciences, Irvine, California) percutaneous annuloplasty system has received CE mark approval for functional MR in Europe. Cardiac imaging pre-procedural assessment and intra-procedural guidance are crucial for procedural success and will be reviewed here.

PATIENT SELECTION

Identification of Valve Morphology

Multiple Societal guidelines (1, 2) recommend identification of the etiology and consequence of MR as the initial step in evaluation. A recent American College of Cardiology (ACC) consensus statement (3) recommend the use of transthoracic echocardiography (TTE) for the initial evaluation of patients with signs or symptoms of MR. Identification of the etiology of MR (primary or secondary) as well as the hemodynamic effects of MR (i.e., on ventricular or atrial size and function) are essential for the selection of the appropriate patient for transcatheter repair procedures. Isolated annular devices are not appropriate for primary disease. Current Societal and

FDA recommendations for use of the edge-to-edge repair system in degenerative disease (Class IIB) include patients who are at high surgical risk with Stage D qualifications including an effective regurgitant orifice area (EROA) of ≥40 mm^2, regurgitant volume of ≥60 cc and regurgitant fraction of ≥50%. Importantly for chronic MR, the left ventricle (LV) should be dilated.

The recent ACC/American Heart Association guideline update (4) as well as the recent ASE updated guideline (5), recommend using the same quantitative criteria for primary as secondary MR to define severe disease: EROA ≥40 mm^2, regurgitant volume of ≥60 cc. Although current European Society of Cardiology guideline (which uses a lower cut-off) (2) are not aligned with the European Society of Echocardiography guideline (which uses the aforementioned cut-offs) (6) both American and European guidelines recognized that worse outcomes for functional MR may be seen with an EROA of >20 mm^2 (2, 4). FDA approval for use of the edge-to-edge repair device for functional MR was based on the results of the Cardiovascular Outcomes Assessment of the Mitraclip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (7). The approved indication thus includes secondary or functional MR include high surgical risk patients with LV dysfunction, moderate-severe or severe MR (EROA ≥30 mm^2), with LV dilatation (LV end-systolic dimension ≤ 70 mm) and LV ejection fraction >20%. Guidelines are expected to change based on the results of the randomized trial and these new indications.

MITRAL VALVE REGURGITATION QUANTIFICATION

Baseline MR should be quantified according to the guidelines described by the American Society of Echocardiography and European Association of Echocardiography (5, 6). A multi-parametric, multi-modality method should always be performed, using both qualitative and quantitative assessment of MR which are well-described in the guidelines. Color Doppler has been an easy and rapid parameter to assess MR severity, making use of the three components of regurgitant jet: proximal flow convergence dependent on both orifice and flow, the vena contracta which can approximate the regurgitation orifice, and jet area which may relate to regurgitant volume. However, the color Doppler parameters are dependent on technical and ultrasound physics parameters, the shape of the orifice as well as hemodynamic variables. Thus, color Doppler measurements are highly variable and may be used to detect the presence of MR but are not recommended as the sole method to document severity (6); the three components should be integrated to improve accuracy (5). As per the society guidelines, MR severity is based on quantitative parameters of regurgitant volume, regurgitant fraction, and EROA. These measurements can be performed by proximal Isovelocity surface area (PISA) method, quantitative Doppler and 3D color Doppler vena contracta planimetry (**Figure 1**). The pitfalls of each method are covered by the guidelines and are beyond the scope of this document (5, 6).

Abbreviations: MDCT, multi-detector row computed tomography; MR, mitral regurgitation; MVA, mitral valve area; TEE, transesophageal echocardiography; 2D, 2-dimensional; 3D, 3-dimensional.

MITRACLIP

Percutaneous edge-to-edge repair with mitraclip is the most common percutaneous mitral repair technique performed worldwide. A recent multi-center clinical study of the German national patient sample included 13,575 implants over 5 years (8). Repair using this device mimics the Alfieri surgical repair. Patient selection and procedural guidance is largely predicated upon 2-dimensional (2D) and 3-dimensional (3D) echocardiographic imaging, particularly TEE. There is currently no role for multi-detector row computed tomography (MDCT) for pre-procedural screening for mitraclip (9).

Procedural Planning

The Mitral Valve Academic Research Consortium (MVARC) definitions of "device success" measured at 30 days are listed in **Table 1** (10, 11). The goal of the procedure is thus to reduce the mitral regurgitation to no greater than mild, recognizing that MR reduction is considered optimal when post-procedure MR is reduced to trace or absent. MR reduction is considered acceptable when post-procedure MR is reduced by at least 1 class or grade from baseline and to no more than moderate (2+) in severity. Recent outcomes data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, showed that reduction to ≤mild (grade 1) disease was dependent on experience (achieved in 66.5% of patients at sites with pre-commercial experience, compared to 57.4% at commercial sites, $p = 0.04$) (12). Sorajja et al. also showed that increased mortality was seen with >mild MR (13). The original EVEREST trial echocardiographic anatomic inclusion criteria included non-rheumatic valve morphology, mitral valve area ≥ 4 cm^2, flail gap ≤ 10 mm, flail width ≤ 15 mm, coaptation depth ≤ 11 mm, coaptation length ≥ 2 mm, and central regurgitation at the A2-P2 interface (29). Case reports, observational studies, and clinical experience have since shown the possibility of successful therapy outside of these original criteria (14–16). Lubos et al. found that effective regurgitant orifice area >70.8 mm^2 and mitral valve area ≤3.0 cm^2 independently predicted clip failure (defined by aborted procedure or inability to reduce MR to ≤ 2+ in severity) (33). A recent paper studying treatment of degenerative MR suggested that higher baseline left-ventricular end-diastolic diameter and mitral annular diameter predict greater than mild residual MR after mitraclip (17). In current clinical practice, absolute anatomic limitations are very few (18). Hahn et al. listed the echocardiographic features associated with ideal, challenging and difficult anatomies (**Table 2**) (18). Severe calcification of nearly the entire leaflet length at the grasping zone, short leaflet length and low baseline mitral valve area (MVA) are the most common current contraindications. Prior research has shown that mitral valve area decreases by ∼50% after a single Mitraclip is placed (19–21). Thus, in general, a baseline MVA >4.0 cm^2 is desirable.

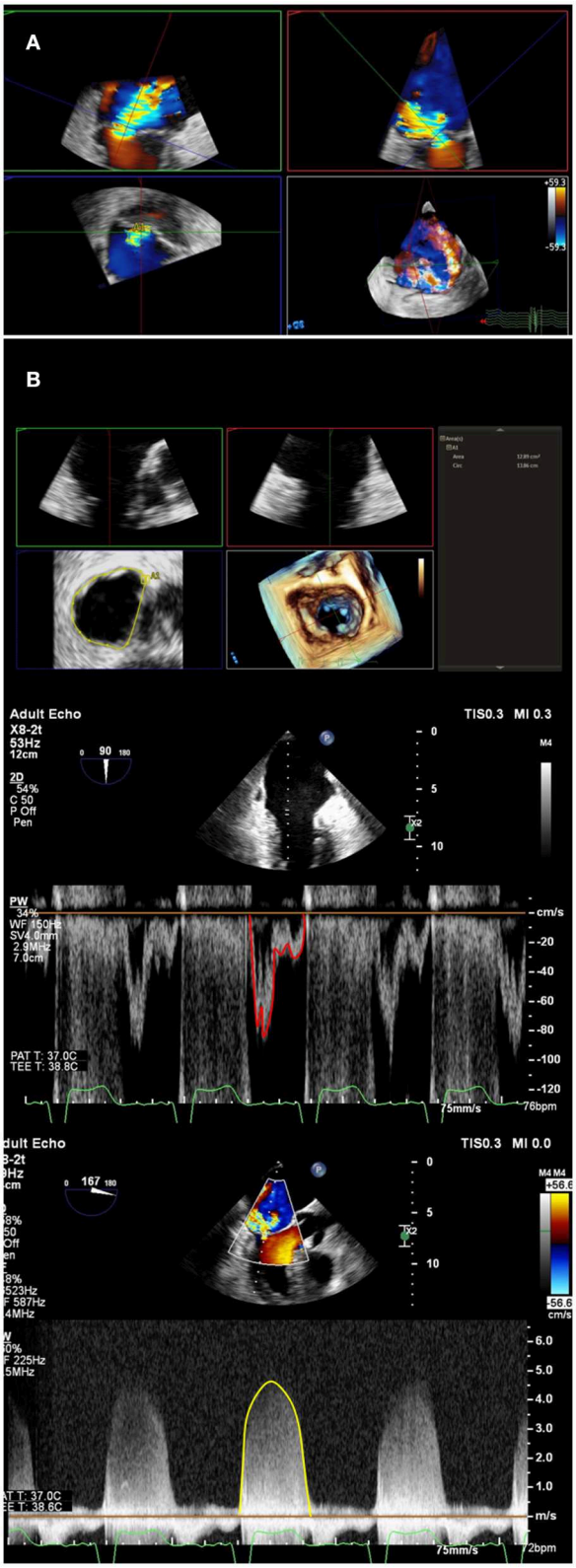

FIGURE 1 | Multi-parametric assessment of mitral regurgitation. In addition to qualitative color Doppler grading, multiple methods of mitral regurgitant *(Continued)*

FIGURE 1 | quantification should be used. **(A)** A multiplanar reconstruction of 3-Dimensional echocardiographic color Doppler can be used to directly planimeter vena contracta area. A double-oblique method is used to align long-axis images (upper left and right), and directly planimeter vena contracta area (lower left). **(B)** Mitral valve inflow stroke volume, which includes mitral regurgitant volume, can be calculated by multiplying mitral annulus area (top panel) by pulsed-wave velocity time integral at the annulus level (middle panel). Left ventricular or right ventricular outflow tract calculated stroke volume, in the absence of aortic or pulmonic insufficiency, can be subtracted from mitral stroke volume to obtain regurgitant volume. Regurgitant volume can be divided by mitral regurgitation continuous-wave Doppler velocity time integral (bottom panel) to calculate quantitative Doppler derived regurgitant orifice area.

TABLE 1 | Definition of device success: This table lists the definition of device success as outlined by Mitral Valve Academic Research Consortium Stone et al. (10).

Device success (measured at 30 days and at all later post-procedural intervals)
All of the following must be present: I. Absence of procedural mortality or stroke; and II. Proper placement and positioning of the device; and III. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and IV. Continued intended safety and performance of the device, including: a. No evidence of structural or functional failure b. No specific device-related technical failure issues and complications c. Reduction of mitral regurgitation to either optimal or acceptable levels* without significant mitral stenosis (i.e., post-procedure mitral valve area is $\geq$1.5 cm^2 with a transmitral gradient <5 mm Hg), and with no greater than mild (1+) para-device mitral regurgitation and without associated hemolysis)
**Mitral regurgitation reduction is considered optimal when post-procedure mitral regurgitation is reduced to trace or absent. mitral regurgitation reduction is considered acceptable when post-procedure mitral regurgitation is reduced by at least 1 class or grade from baseline and to no more than moderate (2+) in severity.*

However, a smaller baseline area may be acceptable in patients with small body habitus if potential benefits outweigh risks.

For patient anatomic TEE screening, mitral anatomy should be completely described, including etiology of mitral regurgitation, specific scallop location(s) of mitral regurgitant jet(s), and leaflet qualities at these locations (thickening, calcification) (**Figure 2**). A biplane evaluation from the commissural view, interrogating the mitral valve across the commissures, is useful to localize anatomy at the grasping location and plan the "grasping view." A wide coaptation gap may necessitate the XTR system, which has longer gripper arms for wider reach. MVA should be planimetered using 3D echocardiography multiplanar reconstruction during maximal or near maximal mitral valve opening in mid-diastole, taking care to measure at the leaflet tips. Care should be taken to reduce 3D volume size to maximize frame rates. Multi-beat or spliced imaging is not typically recommended, as this may create artifacts which will render MVA measurement inaccurate. Currently, 2 versions of the MitraClip are available, the XTR, and NTR. **Table 3** lists specifications and considerations for each version. The XTR has a wider reach and longer clip arms than NTR. Although experience is limited thus far, the XTR is likely better for wide coaptation gaps with a higher risk of chordal

TABLE 2 | Table of echocardiographic features for ideal, challenging and relative contraindications for mitral edge-to-edge repair.

	Ideal echo features	Challenging echo features	Relative echo contraindications
Location of pathology	Segment 2	Segments 1 or 3	• Body of leaflet (i.e., perforation or cleft/deep fold)
Calcification	None	• Mild, outside grasping zone • Extensive annular calcification	• Severe calcification at site of grasping zone
Mitral valve area/gradient	• >4 cm^2 • ≤4 mm Hg	• >3.5 cm^2 and <4 cm^2 with small BSA or mobile leaflets • ≥4 mm Hg	• <3.5 cm^2 and ≥4 mm Hg
Grasping zone length	• >10 mm	• 7–10 mm	• <7 mm
Functional MR	• Normal thickness and mobility • Coaptation depth <11 mm	• Carpentier IIIB (restricted) • Coaptation depth >11 mm	• Carpentier IIIA (rheumatic thickening and restriction)
Degenerative MR	• Flail width <15 mm • Flail gap <10 mm	• Flail width <15 mm with large valve area and option for >1 MitraClip • Flail gap >10 mm with possibility of adjunctive measures	• Barlow's disease with significant regurgitation segments 1–3
Other pathology		• Annuloplasty ring with adequate mitral valve area and length • HOCM with systolic anterior motion • Extreme disease (markedly dilated annulus or EROA ≥70.8 mm^2)	

Reproduced with permission from Hahn RT. Transcathether Valve Replacement and Valve Repair: Review of Procedures and Intra-procedural Echocardiographic Imaging. Circ Res. 2016;119:341-56. BSA, indicates body area; EROA, effective regurgitant orifice area; HOCM, hypertrophic obstructive cardiomyopathy; and MR, mitral regurgitation.

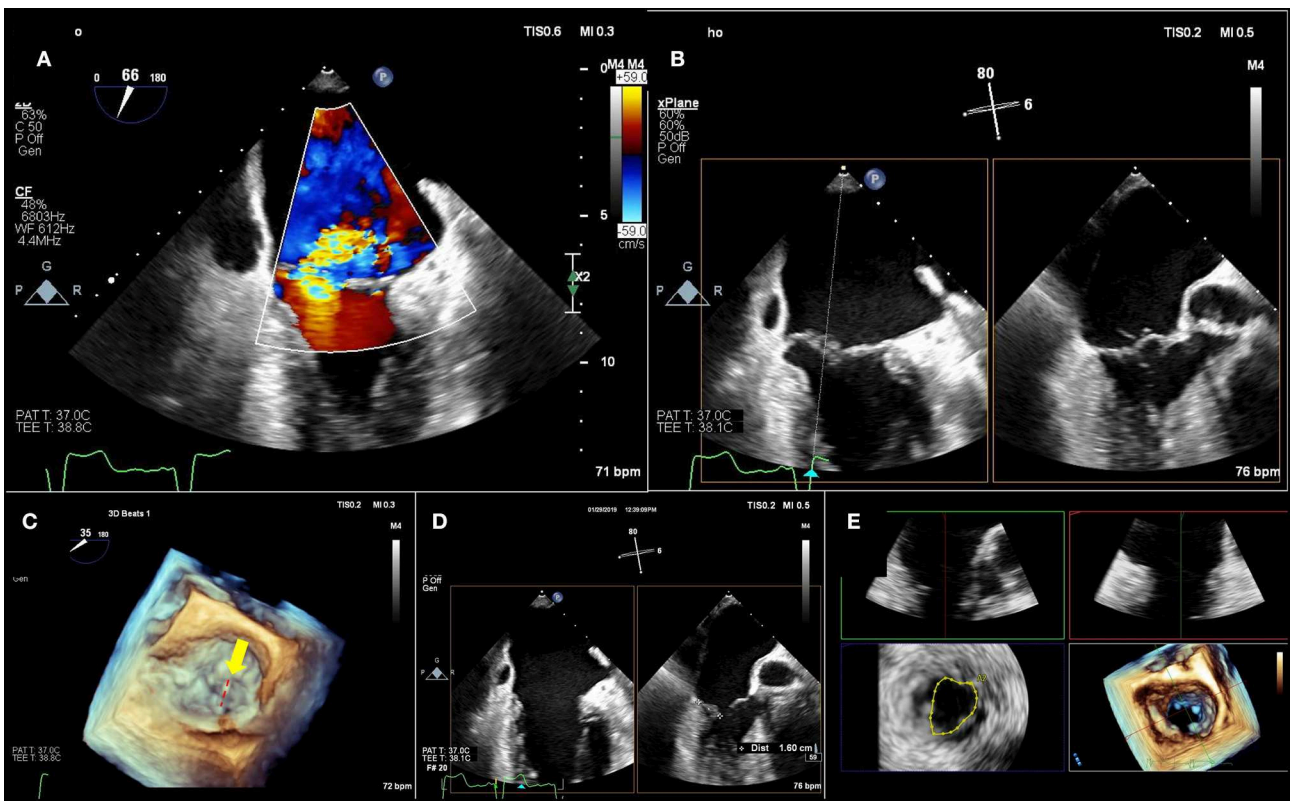

FIGURE 2 | Pre-Mitraclip mitral valve anatomy characterization. **(A)** A large, medial regurgitant jet is demonstrated. **(B)** On bi-plane imaging of the region, medial anterior flail segment is demonstrated. **(C)** A 3-dimensional echocardiographic surgical view demonstrates A2-A3 scallop flail (yellow arrow) with a ruptured chord (red-dashed line). **(D)** Leaflet length in planned "grasping view" is measured and appears adequate for insertion into edge-to-edge repair device. **(E)** 3-Dimensional echocardiographic reconstruction demonstrates adequate baseline mitral valve area of 4.4 cm^2, greater than the 4.0 cm^2 cutoff.

TABLE 3 | Mitraclip XTR vs. NTR specifications and preferred device for specific anatomical considerations.

Specification	XTR	NTR
Closed Clip Length (mm)	18	15
Grasping Width at 120° (mm)	22	17
Clip Arm Length (mm)	12	9
Desired leaflet insertion length (mm)	9	6
Device preferred for anatomical consideration		
Longer leaflet	X	
Large gap	X	
Redundant leaflet	X	
Leaflet calcification		X
Smaller mitral valve area		X
Mitral valve commissures		X

entanglement for lesions at the commissures. Recent experience has been described using XTR in Barlow's disease (22) and as an adjunct after Cardioband (23) and transapical neochord implants (24). Early, compassionate use data have been published using a similar device (25), the Edwards Pascal, and the ongoing CLASP IID pivotal trial will provide further study.

Intra-Operative Imaging Guidance

Intra-operative imaging guidance for MitraClip is predicated upon 2D and 3D TEE imaging. The procedural plan based on screening and intra-operative diagnostic TEE, including location and numbers of clips proposed, should be discussed between the interventional imager and interventional cardiologist. A qualitative and quantitative re-evaluation of the mitral regurgitation intra-procedurally, prior to MitraClip placement, is needed to establish a baseline for comparison at the end of the case. A step-by-step overview of imaging-based procedural steps is outlined in **Figure 3**. The initial, and possibly most important, step, is imaging guidance of the transseptal puncture. The ideal location for transseptal puncture is mid-fossa in a bicaval view, and ∼4–4.5 cm basal from the mitral annulus as visualized in the 4-chamber view. The anterior-posterior rotation of the catheter typically determines the height above the annulus with more posterior positions gaining height. The exact height above the annulus for the transseptal puncture is determined by the planned positioning of the device: less height is required for a lateral defect, and more height is required for a medial defect as deflecting the system toward the mitral annular plane from lateral to medial will move the Mitraclip beyond the mitral annulus if the puncture is too close to the mitral annulus. The superior-inferior position of the catheter determines the position relative to the commissure. Aligning the puncture with the medial commissure facilitates positioning of the device anywhere along the mitral coaptation line. With atrial dilation that is commonplace in this patient population, the location of the interatrial septum to the mitral commissures may be distorted. This distortion is difficult to appreciate on 2D TEE imaging alone; thus, 3D TEE confirmation of transseptal puncture location is recommended (**Figure 3**). Caution is advised as one approaches the borders of the heart, so as not to puncture outside of the cardiac chambers (26). Altiok et al. showed the utility of 3D TEE for Mitraclip procedural guidance by having an interventional cardiologist evaluate 2D vs. 3D TEE for the procedural steps (27). 3D TEE was graded as superior for to 2D TEE for 9 of the 11 procedural steps studied, including transseptal puncture, guidance of the delivery system toward the mitral valve, positioning of the delivery system above the mitral valve, adjustment of the orientation of opened clip arms in relationship to the commissures, visualization of inserted clip position relative to the residual regurgitant jet after clip arm closure, and safe removal of the clip delivery system from the left atrium. 3D TEE was graded as inferior to 2D TEE only for leaflet grasping and evaluation of leaflet insertion. However, more contemporary clinical experience has shown the utility of visualizing a tissue bridge across the grasped leaflets by 3D echocardiography (**Figure 3**).

Post-implant Assessment

Recent guidelines delineate the many pitfalls of routine measures of MR severity following percutaneous edge-to-edge repair (28). Importantly, PISA is not recommended given the assumption of a hemispheric flow convergence, the frequent presence of multiple MR jets and possible acoustic shadowing by the device. Quantitative Doppler also is limited by the presence of the edge-to-edge device and the presence of a double orifice. Thus, despite the multiple limitations of color Doppler parameters, flow convergence, vena contracta width, and jet area must be part of the multi-parametric assessment which should also include:

Mitral and pulmonary vein inflow patterns, change in forward stroke volume, and continuous wave jet profile. The primary quantitative parameter still valid following an edge-to-edge repair is three-dimensional color Doppler direct planimetry of the vena contracta areas (19, 29, 30). 3D color Doppler multiplanar reconstruction may be the method of choice to evaluate residual vena contracta area. In a recent study, final intra-procedural 3D color Doppler planimetered vena contracta area < 27 mm2 was associated with improved New York Heart Association functional class at 30 day follow-up (30). In another study by Altiok et al. left atrial and left ventricular volumes were significantly more reduced at 6 month follow-up in patients in whom 3D-TEE measured vena contracta area was reduced by $>50\%$ (19).

Similarly to the pre-procedural evaluation, residual mitral valve orifice area should be planimetered on 3D multiplanar reconstruction, with each orifice area measured and added to evaluate the total orifice area. If significant mitral stenosis is present by planimetered mitral valve orifice area or transmitral gradient while the clip is attached to the delivery system, the clip can then be released, repositioned and/or withdrawn.

After clips are released from the delivery system, tissue grasp should be reconfirmed, and residual regurgitation, mitral valve orifice area, and transmitral gradient by continuous-wave Doppler should be evaluated. Complications should be monitored on TEE imaging during and after the procedure, including pericardial effusion, clip detachment, and damage to the leaflets or subvalvular apparatus.

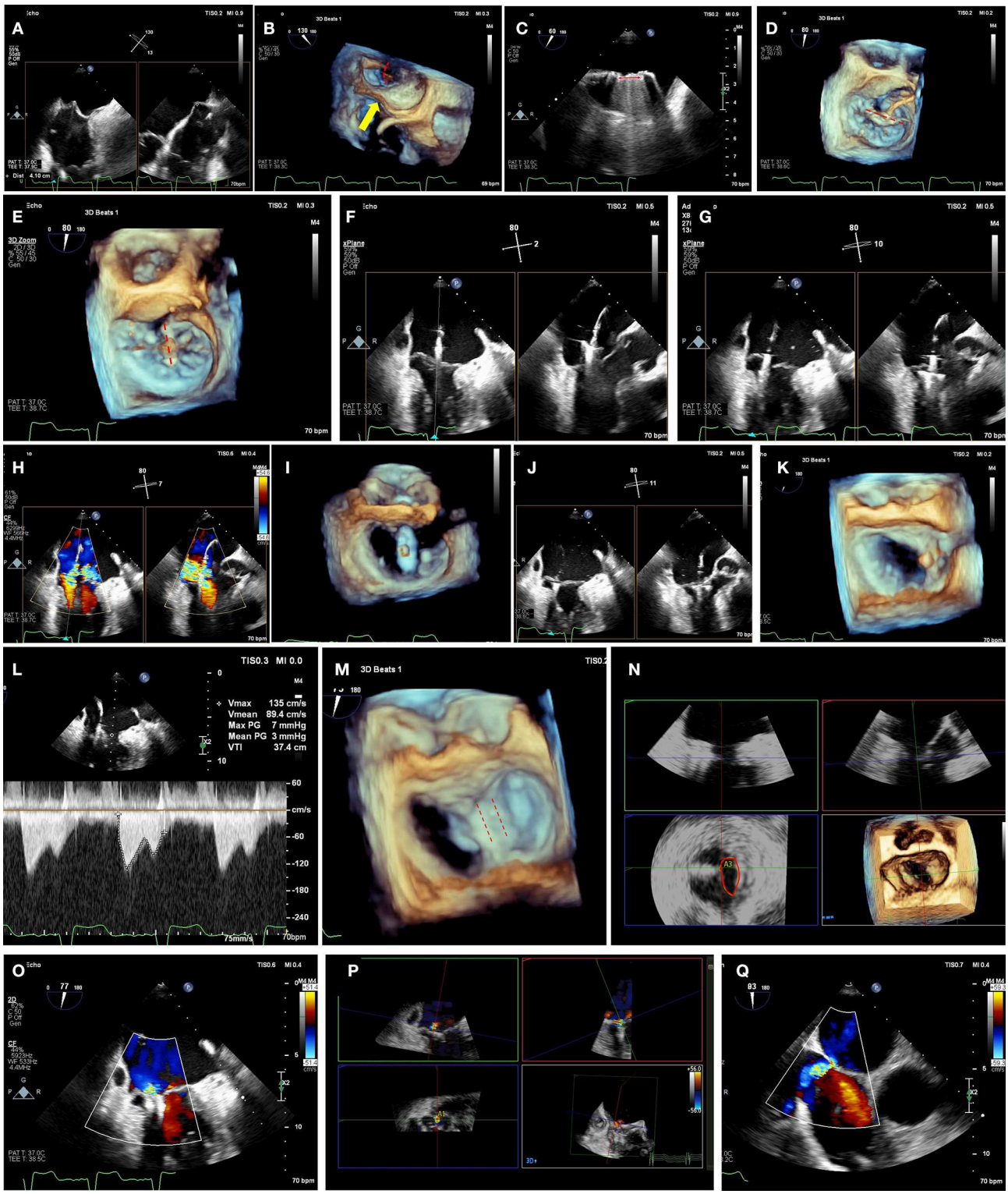

FIGURE 3 | Mitraclip intra-procedural guidance. **(A)** Transseptal puncture should be performed in a mid-posterior location within the inter-atrial septum, 4.0-4.5 cm basal to the mitral annulus plane. Bi-plane imaging allows simultaneous visualization of the bicaval (typically 90–110°) and the 4-chamber (typically 0 or 180°, or orthogonal view from biplane imaging of bicaval view) view for localization of the puncture. **(B)** 3-dimensional echocardiographic imaging of needle tenting at the interatrial septum (yellow arrow) confirms trajectory across the mitral commissures (red dashed arch). **(C)** Extrusion of the mitraclip from the delivery sheath should be

(Continued)

FIGURE 3 | visualized to avoid injury from contact with the atrial wall. **(D)** After straddling the clip delivery system across the mitral commissures, the clip is opened while visualizing the 3D-TEE surgeon's view (left atrial perspective, aortic valve at 12 o'clock position) to check orientation (red-dashed line). In the image shown the clip needs rotation of 90° to achieve appropriate orientation perpendicular to commissures. **(E)** After clockwise rotation, the clip is oriented in planned clipping direction (red-dashed line) on the surgeon's view for A2-A3 flail segment. **(F)** Mitraclip position is confirmed from a bi-plane of commissural and 3-chamber views. On the 3-chamber views, clip arms are well-visualized. The biplane view is particularly useful in a non-central jet, as a traditional 3-chamber view may not demonstrate the grasping direction. Conversely, placing a biplane in the commissural view at the desired grasping location will provide the orthogonal grasping view. **(G)** As the mitraclip passes into the left ventricle, stable orientation and location should be confirmed. **(H)** Clip location is confirmed at the mitral regurgitation jet location by bi-plane color Doppler imaging. **(I)** By reducing gain settings, the clip orientation in the left ventricle can be confirmed by 3-dimensional echocardiographic imaging. **(J)** As the clip is pulled back toward the mitral leaflets, the insertion of each leaflet into each clip arm should be visualized. As the clip arms are fully closed, live color Doppler imaging may also be used to confirm reduction of the mitral regurgitation jet. **(K)** A tissue bridge is seen on 3-dimensional echocardiographic imaging after leaflet clipping, confirming adequate grasp. **(L)** Transmitral continuous-wave Doppler should be used to assess increase in gradients. If there is an unacceptable increase, clip can be released and repositioned or removed if still attached to delivery system. **(M)** After second clip is placed, both clips can be seen (red-dashed lines) on 3-dimensional echocardiographic imaging, with tissue bridge indicating bileaflet grasp of each clip. **(N)** Multiplanar 3-dimensional reconstruction allows for planimetry of each mitral orifice (red oval). Orifice areas are added together to calculated total mitral valve area after clip placement. If area is inadequately small and clip is still attached to delivery system, clip may be withdrawn and/or repositioned. **(O)** Post-clip mitral regurgitation is qualitatively mild by 2-dimensional color Doppler imaging. **(P)** 3-dimensional color Doppler multiplanar reconstruction allows alignment of mitral regurgitant jet(s) and direct planimetry of vena-contracta area (lower left panel), adding multiple jet areas together if needed. **(Q)** After withdrawal of delivery system and guide catheter, an iatrogenic atrial septal defect is visualized with left-to-right shunt by color Doppler. In the absence of right-to-left shunting with drop in oxygen saturation, post-procedural atrial septal defects generally do not require closure.

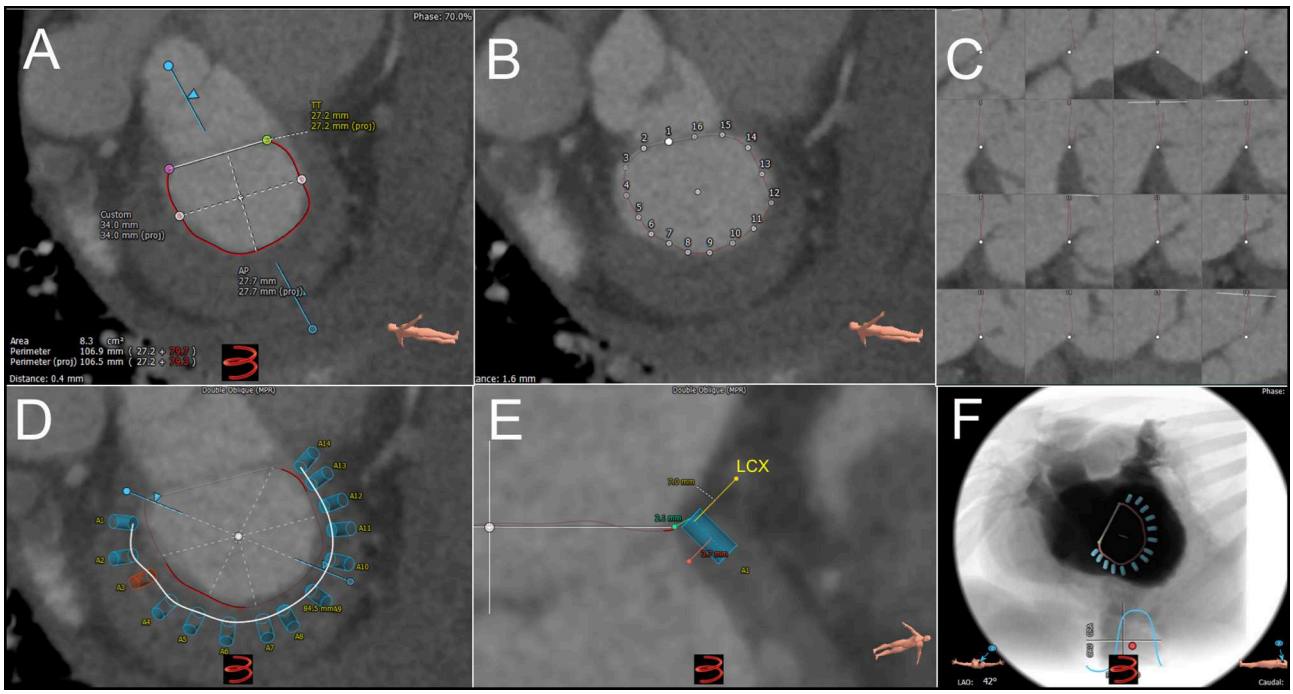

FIGURE 4 | Pre-procedural cardiac computed tomography virtual anchor planning for cardioband. **(A)** Cubic-spline interpolation of multiple points is used in a semi-automated workflow to calculated projected mitral annulus perimeter excluding the trigone-to-trigone distance, which is used for sizing of Cardioband. **(B)** Control points of cubic-spline interpolation are visualized and can be adjusted on the short-axis, or long axis views **(C)**. **(D)** Anchor planning can be performed from trigone to trigone to visualize the trajectory of band. In this image, 14 anchors are planned with a potentially unsuitable location marked as a red anchor. **(E)** Each virtual anchor can be visualized (blue rectangle), and projected distances from anchor head to mitral annulus (turquoise line), mid-anchor to left ventricle (pink line), and nearby blood vessels such as the left circumflex coronary artery (yellow line) can be measured. **(F)** Projected fluoroscopic views can be planned.

CARDIOBAND

The Cardioband mitral annuloplasty system has been described in detail elsewhere (31). In short, this system is composed of a series of metal anchors contained within a Dacron band which are implanted in step-wise fashion around the circumference of the mitral annulus. After the last anchor is placed, the device is cinched for annular reduction. This mimics surgical annuloplasty. Early experience has been promising (31, 32). Recently, the single-arm, multi-center European trial showed reasonable safety and efficacy with a significant reduction in septolateral diameter by echocardiography from 3.7 ± 0.4 to 2.6 ± 0.4 ($p < 0.01$) immediately post-procedure, which was maintained at 1 year follow-up (32). The Annular Reduction for Transcatheter Treatment of Insufficient Mitral Valve Pivotal randomized, controlled clinical trial comparing a combination

of Cardioband repair and guideline directed medical therapy against guideline directed medical therapy alone is ongoing in the United States.

Procedural Planning

All patients receiving mitral Cardioband should undergo preprocedural TEE (with 2D and 3D imaging) as well as MDCT. Mitral regurgitation etiology and severity should be assessed on TEE imaging as previously described. Preprocedural anatomic planning is primarily based on MDCT. MDCT analysis for Cardioband requires a dedicated software module such as those found on 3mensio (Pie medical imaging, Maastricht, Netherlands). Posterior mitral annulus perimeter (excluding trigone-to-trigone distance) should be measured using a cubic-spline interpolation measurement from a semi-automated workflow (**Figure 4**). The length of the implant and number of anchors is determined from the perimeter measurement (**Table 4**). Width of the annular shelf should be evaluated around the proposed implantation circumference on MDCT and TEE to determine whether adequate tissue for anchoring is present. When modeling device implantation on MDCT, anchor implantation angle of 30–60° is expected. Acceptable parameters are thought to include mid-anchor to LV distance of >4 mm and anchor head to mitral leaflet hinge point distance of <8 mm. These imply enough tissue in the mitral annulus for implantation as well as adequate distance from the leaflet to ensure annular reduction. Given the proximity of the left circumflex coronary artery to the mitral annulus, an anchor to left circumflex distance of >2.5 mm is desired. The coronary sinus location should also be noted, as it may also be injured if close to the proposed anchoring location. The optimal position for transseptal puncture may be planned for each patient from CT analysis.

TABLE 4 | Edwards cardioband sizing chart.

Deployment length by CT (mm)	Implant size	Total anchors required
73–80	A	12
81–88	B	13
89–96	C	14
97–104	D	15
105–112	E	16
113–120	F	17

CT, computed tomography.

Intra-Procedural Guidance

Intra-procedural Guidance of mitral Cardioband is based on 2D and 3D-TEE, and fluoroscopy. Intracardiac echocardiographic imaging may play an increasing role as technology improves. As with Mitraclip, an initial intra-procedural baseline assessment of mitral regurgitation severity, mitral valve orifice area, and transmitral gradients should be performed for direct comparison post-implant. Additionally, baseline mitral annulus dimensions should be recorded for direct post-implant comparison. Transseptal puncture should be 3.0–4.5 cm above the mitral annular plane, and entering the atrium across the anteroseptal commissure on 3-dimensional TEE surgical (en-face) view. The

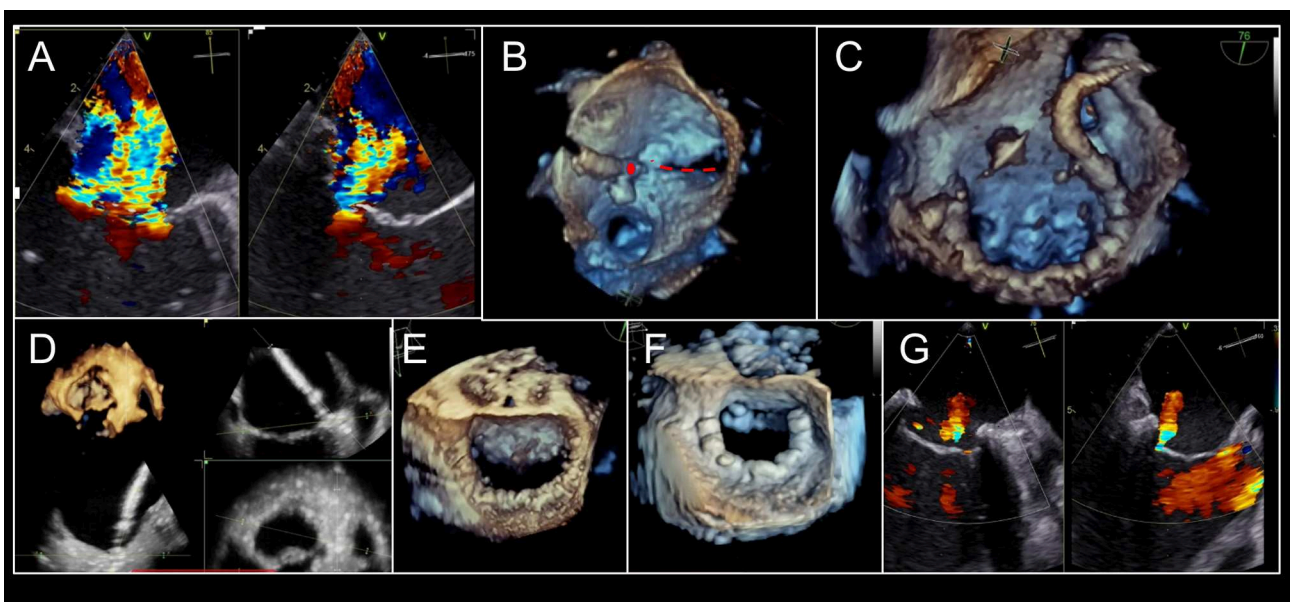

FIGURE 5 | Intra-procedural echocardiographic guidance for cardioband procedure. **(A)** Severe, functional mitral regurgitation is shown in biplane, color Doppler imaging. **(B)** After transseptal puncture, the first anchor (red circle) is implanted adjacent to the lateral commissure (red-dashed line). **(C)** Cardioband implantation continues adjacent to P3 scallop. **(D)** At each anchor implantation, multiplane 3D imaging is helpful to locate position of anchor insertion within the mitral annulus, with adequate distance from leaflet. **(E)**. Completed Cardioband pre-cinching is shown. **(F)** After cinching, annuloplasty reduction is achieved. **(G)** Post-implant mitral regurgitation appears mild by qualitative assessment. 3-dimensional color Doppler multiplanar reconstruction may be used to planimeter vena contracta area. *Images courtesy of Dr. Florian Deuschl*.

first anchor is implanted as anterior as possible to the lateral commissure near the trigone. The positioning of the guide toward the first anchor location can be performed using 3D-TEE (**Figure 5**). Once the correct location is reached, 2D-TEE single and live multiplane imaging should then be used to confirm delivery system location upon the mitral annulus, with care taken to avoid implantation in the base of the leaflet. Each anchor is progressively deployed from the first location posteriorly until the medial commissure/trigone is reached. Before the release of each anchor, a pull test is performed. TEE and fluoroscopic confirmation of tissue anchoring is visualized. Once all anchors are deployed and confirmed and the implant contracted, a post-procedural TEE assessment of mitral annulus dimensions and mitral regurgitation severity should be performed. 3D-TEE multiplanar reconstruction of mitral annulus dimensions, mitral valve orifice area and regurgitant orifice area is ideal for direct comparison to pre-procedural measurements. As progressively tighter levels of cinching may be performed, these parameters should be assessed after each cinch to ensure adequate reduction of MR without excessive reduction in mitral valve area and/or excessive increase in transmitral gradients.

CONCLUSIONS

The newly established percutaneous mitral valve repair technologies rely heavily on multimodality cardiac imaging for pre-procedural patient selection, as well as for intra-operative imaging guidance. Cardiac imaging will continue to play a critical role in the success of these procedures.

DISCLOSURE

OK reports speaker fees from Edwards Lifesciences; consulting for Jenavalve and Cephea Valves. RH reports speaker fees from Boston Scientific Corporation and Baylis Medical; consulting for Abbott Structural, Edwards Lifesciences, Gore & Associates, Medtronic, Navigate, Philips Healthcare and Siemens Healthcare; non-financial support from 3mensio and GE Healthcare; is Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she receives no direct industry compensation.

AUTHOR CONTRIBUTIONS

OK and RH both conceived the design of the document and approved the final document. OK drafted the document with significant edits and additions made by RH.

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REVIEW
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Complications Following Percutaneous Mitral Valve Repair

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Mitral valve disease affects more than 4 million people in the United States and it is the second most prevalent valvulopathy in Europe. The gold standard of treatment in these patients is surgical repair or mitral valve replacement. In the last decade, numerous transcatheter therapies have been developed to overcome the increased number of subjects with symptomatic severe mitral regurgitation and high surgical risk. The Mitraclip (Abbott Vascular, Menlo Park, CA), PASCAL (Edwards Lifesciences, Irvine, CA, USA), the Carillon™ Mitral Contour System™ (Cardiac Dimension Inc., Kirkland, WA, USA), the Mitralign™ (Mitralign, Tewksbury, Massachusetts), and the Cardioband (Edwards Lifesciences, Irvine, CA) are the principal percutaneous devices for mitral valve repair. We present an evidence-based clinical update that provides an overview of these technologies and their potential complications.

Keywords: mitral valve (MV) repair, complications, transcatheter interventions, MitraClip®, Carillon device, Mitralign, Cardioband

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INTRODUCTION

The prevalence of mitral regurgitation (MR) is continuously increasing and it became the most prevalent valvulopathy in patients older than 75 years of age in the United States and the second in Europe (1). Surgical repair (when the likelihood of successful repair is high) or replacement is the standard therapy for patients with severe MR (2). Nevertheless, in elderly patients with multiple comorbid conditions, cardiac surgery has a high mortality rate. In the last decade, numerous transcatheter therapies have been developed to overcome the increased number of subjects with symptomatic severe MR and high surgical risk. Percutaneous edge-to-edge procedure- the Mitraclip (MC), with more than 80,000 treated patients is so far, the most well-known percutaneous mitral intervention for MR. Previous trials and studies showed that MC is a safe procedure (3–6). Percutaneous mitral annuloplasty using the Carillon™ and the Cardioband device showed also encouraging results with a low complication rate which can vary from one to another study and it may be related to the operator experience and mitral valve (MV) complexity.

The Mitraclip Device and New Generation System 3.0

Similar to the previous versions (first-generation and NT), the MC XTR device consists of two main steering components: a 24-F steerable guide catheter (SGC) and a steerable clip delivery system (CDS), with the implant attached at its tip. The rotational knobs on the handles controlling the flexion mechanism of the guide catheter and CDS are similar to the previous versions of the system. The changes made in the clip delivery catheter have the objective of facilitating better stability and minimize unintended translation of the clip during rotation of the CDS. The steerable sleeve has also been adapted to facilitate response to the rotation of the M-knob.

The mechanism and material of the lock line have been modified (braided polyester core surrounded by high–molecular weight polyethylene), enabling the system to be operated in the "unlocked" position.

The substitution of the gripper material from Elgiloy to Nitinol had supposed a higher deeper gripper drop and facilitated the grasping angle.

The new XTR clip is 5-mm longer than the previous generation. The extended arm's length is 22 vs. 17 mm (the older version).

Following femoral vein puncture, adequate access preparation, and transseptal puncture, the SGC is advanced into the right atrium in a straightened position and then inserted 2–3 cm into the left atrium in the neutral position. Once the SGC has been placed, the CDS is inserted and straddled to enable the steering of the device with ease.

Straddling is performed carefully under fluoroscopic and echocardiographic guidance to avoid perforation of the left atrial wall, left atrial appendage, and surrounding structures.

The alignment of the CDS, perpendicular to the mitral coaptation plan is performed and the clip arms (closed up to 60°) are advanced into the left ventricle (LV). The perpendicularity must re-assess before leaflet grasping. Following, both the leaflets "lapping" into the clip arms should be seen ensuring adequate leaflet insertion. Once the final position is achieved, an exhaustive assessment of the result (degree of MR, final mitral gradient) is performed, followed by the clip release.

Complications During Mitraclip Procedure

Since the first case in 2003 up to now, more than 80,000 MC procedures have been performed. The first trial EVEREST (7, 8) has clearly shown the safety of the device. Moreover, both randomize trials (3, 5, 7, 9) and "real world" registries (4, 6, 10, 11) confirmed that the MC procedure is safe with a high percentage of acute procedural success and minimal complications. The Mitraclip device suffered modifications over time, in order to solve some limitations and potential complications. The presented complications are almost all related to first and second generation of the Mitraclip device and they can be divided into complications related to the catheterization and complications related to the device implantation (**Table 1**).

Complications Related to the Catheterization

Vascular Complications

Vascular complications following large-bore venous puncture are infrequent compared to large diameter arterial sheaths (10, 12), nevertheless, optimal access site management in percutaneous MV repair is fundamental. Vascular access complications may occur due to the proximity of the vein to the femoral artery. Inflammatory processes, surgery near the groin may create fibrotic tissue, which could involve both femoral artery and vein. During the 24F sheath's advance, the force applied in the groin may damage the femoral artery (**Figure 1**). Moreover, fibrotic adhesions between the artery and vein, combined with tortuosity and calcification may impede the sheath's advance and kink (**Figure 1**). Echo guided puncture, may help to identify the proper access site spot and it can be useful also in cases where the femoral vein is located below the artery. Moreover, due to the elastic venous wall properties, the access site sealing and healing is fast and standard manual compression is an effective and safe method in achieving hemostasis. However, several studies have shown that temporary figure-of-eight suture (Z-suture) is a useful tool in achieving hemostasis by compression of the femoral vein through wrapped and folded subcutaneous soft tissue (14). On the other hand, preclosure suture with the Proglide® (Abbott Vascular Inc., Santa Clara, California) device for larger-sized venous sheaths proved to be safe and allowing an early mobilization (15).

Major Bleeding Requiring Transfusion

Although bleeding ranges among the most frequent peri-interventional complications, studies show variable incidences depending on the cohort and definition used, being from 1 to 7.4% (10). It is somewhat intuitive to suspect that bleeding after the MC therapy may arise from the large-caliber femoral venous access, which is required for the 24F guiding sheath. Moreover, a large burden of patients is under anticoagulation therapy and peri-procedural administration of heparin to obtain an activated clotting time (ACT) of more than 250 s increases the risk of access site-related bleeding.

Körber et al. (16) showed in a "real-world registry" that only a third part of the bleedings are related to the access site and the patients with "obscure bleeding" had worse outcomes.

Pericardial Tamponade

The risk of pericardial tamponade is low (10) suggesting that transseptal puncture followed by the advancement of the 24F guiding sheath is safe. As in any other procedure in the initial phase of the learning curve, the rate of pericardial tamponade was a little higher (2.8%), reducing to 0% in the recent studies (13). Nowadays, echo guided transseptal puncture aiming to achieve a posterior and superior position is the main key to avoid potential complications. Although the echo guided transseptal puncture, is a straight step during the MC procedure, sometimes it can be challenging in cases of the thick or very floppy septum, post-surgery septum or in cases with chest wall deformities.

Ischemic Events: Myocardial Infarction, Pulmonary Embolism, Stroke

Percutaneous MC procedure involves the use of potentially thrombogenic materials through the venous system, transseptal advancement of large-bore catheter devices and beating-heart maneuvering of the clip within complex anatomy of the MV and subvalvular apparatus. However, the rate of the ischemic events as myocardial infarction, pulmonary embolism, and stroke is anecdotic and it is usually multifactorial (**Table 1**). On the other hand, comparing with other percutaneous structural procedures, the stroke is a rare complication after TMVR; only an incidence of 0.9% of ischemic stroke was documented on 30 days follow-up in the EVEREST RCT trial (3), 2.6% in the EVEREST-HRR (17) and 1.4% in the MTRA-FR trial (9).

Moreover, during the MC device manipulation, there is a small chance of air embolization into the coronary artery (inadequate

TABLE 1 | Complications during and after Mitraclip implantation.

Complications	EVEREST phase I (8)	EVEREST (7)	TCVT (12)	GRASP (6)	ACCESS-EU (4)	TRAMI (10)	TVT (11)	COAPT (5)	MITRA FR (9)	Mitra expand (13)
Type of study	Trial	Trial	Registry	Registry	Registry	Registry	Registry	Trial	Trial	Registry
Year of publication	2005	2009	2014	2013	2013	2015	2017	2018	2018	2019
Used devices	1st gen	1st gen	1st gen	1st gen	1st gen	1st gen	1st gen	1st and 2nd gen	1st and 2nd gen	3rd gen
Number of patients	27	107	628	117	567	828	2952	302	144	107
Related to the catheterization										
In-hospital death	0%	0.9%	2.9%	0.9%	3.4%	2.2%	2.7%	Data not available	Data not available	0.9%
Need for resuscitation	0%	Data not available	Data not available	Data not available	1.8%	0.8%	Data not available	Data not available	0%	Data not available
Stroke	0%	0.9%	0.2%	0.9%	0.7%	0.9%	0.4%	0.7%	1.4%	0%
Myocardial infarction	0%	0%	0%	0%	0.2%	0%	0.1%	0%	0%	0%
Pulmonary embolism	0%	0%	0%	0%	0.2%	0%	Data not available	0%	0%	Data not available
Acute renal failure	0%	0%	0%	0%	4.8%	0.7%	Data not available	Data not available	Data not available	1%
Major bleeding requiring transfusion	3%	3.7%	1.1%	Data not available	Data not available	7.4%	3.9%	Data not available	3.5%	1%
Major vascular complications	0%	Data not available	0.7%	Data not available	Data not available	1.4%	1.1%	Data not available	Data not available	Data not available
Pericardial tamponade	0%	2.8%	1.1%	0%	1.1%	1.9%	1%	Data not available	1.4%	0%
Dislocation of existing pacemaker lead	0%	Data not available	Data not available	Data not available	Data not available	0%	Data not available	Data not available	Data not available	Data not available
Endocarditis	0%	0%	0%	Data not available	Data not available	0%	Data not available	Data not available	Data not available	Data not available
Related to the clip implantation										
Single-leaflet device attachment	0%	2.8%	Data not available	Data not available	4.8%	2%	1.5%	Data not available	Data not available	4%
Clip embolization	0%	0%	0.7%	Data not available	0	0%	0.1%	Data not available	Data not available	0%
Early partial leaflet detachment*	11%	9%	Data not available	Data not available	0.2%	2%	Data not available	Data not available	Data not available	0%
Thrombus formation on clip	0%	Data not available	Data not available	Data not available	Data not available	0.1%	Data not available	Data not available	Data not available	0%
Isolated leaflet damage	0%	Data not available	Data not available	Data not available	Data not available	Data not available	Data not available	Data not available	Data not available	2%
Relevant mitral stenosis	0%	Data not available	Data not available	Data not available	Data not available	0.5%	Data not available	Data not available	Data not available	Data not available
Conversion to open heart surgery	0%	1.8%	0%	0%	0%	0%	0.7%	Data not available	0%	4%
No procedural success**	3%	26%	4.6%	0%	9%	3.4%	8.2%	2%	4.2%	7%
Cardiac surgery during the first 30 days	3%	0.9%	0%	0%	Data not available	0.9%	Data not available	Data not available	0%	Data not available

**During procedure or up to 30 days-follow-up.*

***According to the operator criteria.*

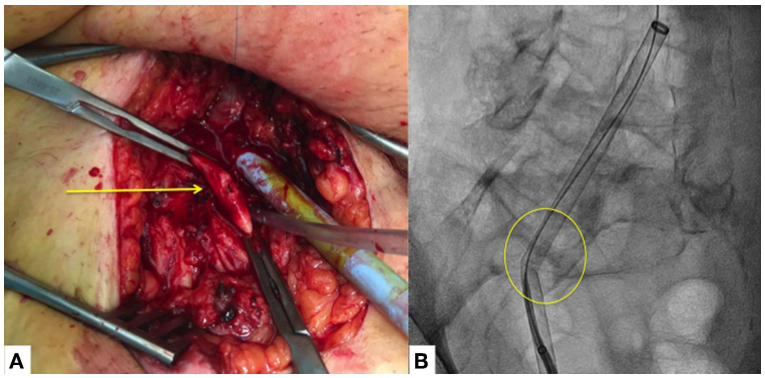

FIGURE 1 | Vascular access complications. **(A)** Major vascular access complication with small laceration of the femoral artery with important fibrotic (adhesions) tissue (yellow arrow). **(B)** Sheath's kinking which does not allow the advance of the transeptal puncture catheter (yellow circle), due to important adhesions between the femoral artery and vein with severe calcified and tortuous iliac artery.

device preparation), which can produce transitory ischemia that can be treated with high oxygenation and intracoronary nitroglycerine. Thrombus forming within the delivery system can have catastrophic consequences and should be avoided by constantly flushing the catheters as well as by aiming for a high level of anticoagulation during the procedure (the ACT between 250 and 300 s). Some cases with post-interventional thrombus formation in the left atrium (LA) and LV or on the MC device have been reported (18, 19). The prothrombotic state related to thrombus formation into the LA may be produced by the disappearance of severe MR jet agitated blood stasis in LA cavity, endocardial damage during septal puncture, and the duration of the Mitraclip procedure (19).

Although there are not any strict recommendations regarding antiplatelet or anticoagulation regimens post-procedure, patients on anticoagulation treatment continue with it and for the rest of the patients double antiplatelet therapy is encouraged during at least 1 month.

Acute Renal Failure

The MC implantation procedure, does not, in itself, require the administration of contrast medium; therefore the acute renal failure is rare. The only study that showed a higher rate of acute renal impairment (4.8% at 30 day follow-up) was ACCESS-EU registry (4), which can be explained by the fact that almost half of the patients presented renal insufficiency at the baseline and it was more prevalent in patients with functional MR and low ejection fraction.

Dislocation of Existing Pacemaker Lead

Often, patients with mitral regurgitation, low left ejection fraction, and LBBB require defibrillators or resynchronization therapy implantation, whose cables may interfere during transseptal puncture and SGC advancement. To avoid this potential complication, it is important to double-check with fluoroscopy and echo the relation between the transseptal puncture catheter or GSC and the cables during maneuvering through the right atrium.

In-hospital Death and Need for Resuscitation

Even though these are high-risk patients, the procedure itself, has a mortality rate between 0–3.4%. Patients with very low cardiac output, severe right ventricle dysfunction, and severe pulmonary hypertension are more prone to adverse events. Moreover, the available data showed a very low rate of the need for resuscitation.

Complications Related to the Mitraclip Device Implantation

Compared with the restrictive inclusion criteria of the EVEREST trial (20, 21), nowadays more patients with challenging anatomy are referred for percutaneous edge-to-edge repair (22). Except for a mitral valve orifice area (MVOA) <4 cm^2 in COAPT, no specific anatomic exclusion criteria are applied in the most recent randomized trials, MITRA-FR (9) and COAPT (5). The third-generation of the MC device was built to overcome the need to treat even more complex cases with longer, redundant or restricted leaflet and large flail.

It is logical that the greater the complexity of cases, the greater the number of complications, but recent studies did not prove this theory (13). Nevertheless, challenging cases should be done by experienced operators in order to keep procedure safe.

Single-Leaflet Device Attachment (SLDA)

It is the most frequent complication with ranges between 0 and 4.8%. SLDA is defined as the loss of the insertion of a single leaflet from the MC device with the ongoing insertion of the opposing leaflet.

It can be acute (during the procedure), subacute (during the first days after the procedure) or late (seen during the follow-up). The majority of the described cases were seen during the procedure and in most cases, it was resolved with second clip implantation.

In the feasibility Everest Trial (7), SLDA occurred in 10 patients (9%), three of them during the procedure, in 1 before hospital discharge, in 5 patients between discharge and 30 days and only 1 partial clip detachment occurred after 30 days. On the other hand, the ACCESS-EU study, which included a large

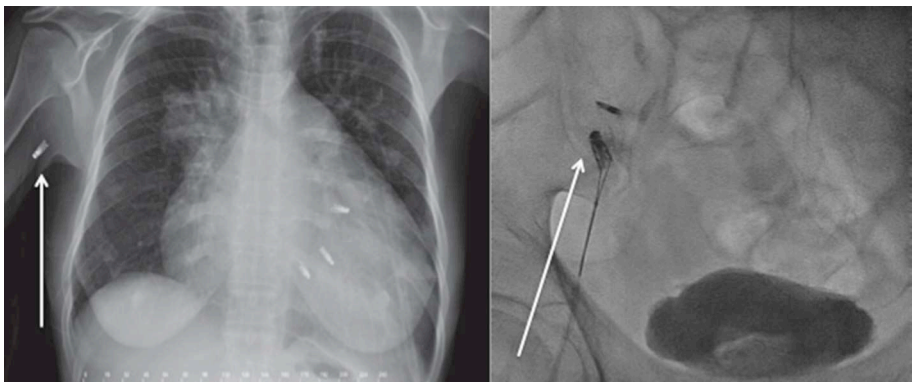

FIGURE 2 | Late Mitraclip embolization. **(Left)** Clip embolization into the axillary artery *Courtesy Dr. Bilge*. **(Right)** Clip embolization into the femoral artery.

number of patients, showed an SLDA of 4.8%, all most during the first 6 months follow-up. Of these cases, 40% were conservatively managed, another 40% had received another MC device and in 6 cases mitral surgery was needed. Nevertheless, there was no need for urgent surgery or intervention. In the recent, all-comers registry published by Praz et al. (13) the rate of SLDA was also 4%, besides the use of the third-generation MC. The most important step is to perform a meticulous echocardiographic assessment during and after grasping of the leaflets and to ensure proper leaflet insertion into the clip arms.

Clip Embolization

MC detachment mostly occurs during the deployment of the clip and is recognized immediately, requiring surgery for its removal. Complex mitral anatomy, several clips implantation with suboptimal echocardiographic window due to the artefacts of the other clips, may be related to clip embolization. Nevertheless, the only two registries that reported clip embolization were the TCVT (12) and the TVT registry [(11); **Table 1**], whose rate of embolization was <1%. Only a few cases were reported and there are no clear guidelines regarding its management. In late embolization, the clip generally migrates through the arterial system and its removal should be done in case if it induces ischemia [(23–25); **Figure 2**].

Thrombus Formation on the Clip

During the MC procedure, an ACT between 250 and 300 s should be achieved (26). There are no strict recommendations regarding the antiplatelet therapy and in general, the patients do not receive the loading dose. The thrombotic status may determine thrombus formation beside correct anticoagulation, especially in patients with a very low cardiac output and blood stasis.

Isolated Leaflet Damage/Tearing

Complex mitral anatomy as severe prolapse, degenerative, or calcified leaflets are more prone to the leaflet damage (27). Sometimes several grasping maneuvers are needed to find a proper clip position, which can damage the ill tissue. Moreover, there are cases where more than one clip is needed to achieve an adequate reduction of MR. Second or third clip implantation is more challenging; because the additional clip is advanced closed in the left ventricle and sometimes the perpendicularity can be lost. In those cases, the clip arms must be everted and withdrawn into the LA. This procedure may harmful and it may produce leaflet tearing or chord rupture. Isolated leaflet damage was described in 2% of patients using the third generation of the MC device (13). In the presence of bigger clip arms, maneuverability is more difficult and there is a higher chance to clip entrapment. Solving isolated leaflet damage is complex, and due to the presence of severe residual mitral regurgitation, in most of cases surgery is required. If the mitral anatomy is favorable (large mitral valve, enough tissue), additional clips can be implanted to stabilize the damaged leaflet. When there is an important gap between the clips, generating a severe mitral regurgitation and another Mitraclip is impossible to implant, an Amplatzer device could be placed to cover the hole (28). Kubo et al. (29), showed in a case series of 9 patients that this technique using an ADO II device is relatively safe and with good results at short time follow-up. Nevertheless, the main complications are device embolization and hemolysis (29).

Relevant Mitral Stenosis

In daily practice, it is a common problem for the interventional team to accept a higher transmitral valve gradient for better mitral regurgitation reduction during an MC procedure. TRAMI registry is the only one (10), which presented the rate of relevant mitral stenosis. The rest of the studies just reported the mean transmitral gradient after MC implantation. It is known that patients with relevant mitral stenosis after MV repair had a worse quality of life (30). A mean gradient of more than 5 mmHg is considered not acceptable and it is mainly related to a baseline MVOA <4.0 cm^2 and with 2 or more clips implantation (31). Before releasing the clip, the echocardiographic assessment is crucial to determine the mitral regurgitation and stenosis. In case of a high mitral gradient with a mitral area <4 cm^2, the clip should not be implanted. In the other case, in the presence of a high gradient but a mitral area more than 4 cm^2, the clip should be repositioned. Moreover, continuous left atrial pressure measurement may be useful for decision making during Mitraclip. The mitral regurgitation is correlated with

immediate decreases in LA v-wave pressure, LA mean pressure, and left ventricular (LV) end-diastolic pressure (including when LA pressures were indexed to LV pressures to account for changes in afterload) (32). In case of residual MR after implantation of a clip, operators have to decide between clip repositioning or implantation of an additional clip. If the indexed LA mean pressure increases during an additional clip implantation, it should be removed and probably respect the residual MR. If not, an additional clip could be implanted to limit the degree of residual MR.

Conversion to Open Heart Surgery

Conversion to open-heart surgery is a rare complication and is it mainly related to the complications mentioned above as clip embolization or MV-injury with severe MR that cannot be treated by clip implantation.

No Procedural Success

The rate of no procedural success is between 0–26%. Nevertheless, there is a big variability regarding the definition of no procedural success and it is left to the operator to decide it. The technical success depends on different variables, the mitral anatomy, the operator experience, and the used device. The new device generation is easier to work with and the movements are better transmitted to the clip. After the first feasibility study, the acute procedural success was always more than 90%, besides of more complex cases.

Pascal Device

The novel Edwards PASCAL transcatheter mitral valve repair (TMVr) system (Edwards Lifesciences, Irvine, CA, USA), similar to Mitraclip device mimics the classical Alfieri stich; nevertheless its design seems to overcome the limitations that have been seen with Mitraclip. The Pascal device improves the reduction of mitral regurgitation through implementation of a central spacer, and allowing for independent leaflet grasping.

It consists of a 10 mm central spacer that acts as filler in the regurgitant orifice of the mitral valve, and is attached to the valve leaflets by two paddles and clasps. The steps of procedure are similar to Mitraclip, with transseptal puncture, aiming a height between 4–5 cm. Nevertheless, the principal advantage of this novel system is the clasps, which can be, operated either simultaneously or independently to facilitate leaflet capture in complex anatomies. The convex curvature of the tip of the paddles aims to reduce tension on the valve leaflets.

Complications Following PASCAL Transcatheter Mitral Valve Repair System Implantation

Up-to-date only 100 cases with severe mitral regurgitation were performed with the Pascal device. The first-in-man study including 23 patients, showed encouraging results at 30-days follow-up (33). The complications derived from procedure were a minor bleeding and a transient ischemic attack. Cardiovascular morality at 30-days was 9%, and in one case partial leaflet detachment was seen postmortem.

The CLASP Study (NCT03170349) is a multi-center single arm, study to evaluate the safety, performance and clinical outcomes after Pascual device implantation in patients with severe mitral regurgitation. The preliminary results are available in 60 patients. Cardiovascular morality was 1.6%, and without any stroke, myocardial infraction or cardiac tamponade. Severe bleeding was present in 6.5% (n: 4) of patients and only in two of them it was related to the access site complications. Re-intervention was needed in one case (34).

Carillon System Device

The Carillon^{TM} Mitral Contour System^{TM} (Cardiac Dimension Inc., Kirkland, WA, USA) is a device designed for indirect percutaneous MV annuloplasty through the coronary sinus (CS) of symptomatic patients (NYHA class III-IV despite optimal medical therapy) with dilated cardiomyopathy and moderate-to-severe functional MR. The device received the CE mark in August 2011. The implant features a wire-shaping ribbon (connector), positioned between two interwoven anchors to form a semi-helical shape. The shaping ribbon is designed to be deployed, tensioned, and fastened (percutaneously through the right internal jugular vein- IJV-) inside the CS with the aim to reshape the mitral annulus (MA) favoring leaflet coaptation. Indirect annuloplasty exploits the anatomical position of the CS, which embraces approximately two-thirds of the posterolateral MA from whom it is separated by myocardial tissue. The CS shortening (theoretically) obtained by the tension applied to the device may induce the consequent reduction of the area of the MA. The procedure is performed under general anesthesia and it is fluoroscopic and transoesophageal echocardiography (TOE) guided. An emergency surgical back-up room is needed in case of complications (any emergent conversion was actually reported).

Complications Following Percutaneous Indirect Mitral Annuloplasty Using the Carillon™ System

The procedure itself is relatively quick (median total procedure time 102 min from first sheath insertion until the last catheter is removed from the body) (35), safe and less invasive compared to other percutaneous MV repair procedures. However, several complications were reported.

Contrast-Induced Nephropathy (CIN)

The Carillon implantation procedure, does not, in itself, require the administration of a significant amount of contrast medium but several injections of contrast dye are required to assess the anatomical features of the CS, the coronary artery anatomy and its relation to the CS and to guide the implantation of the device within the CS (median contrast volume injection 186 $\pm$ 93 ml) (35). Cases of CIN after implantation of the Carillon have been reported (36, 37). Although it is about a severe mitral regurgitation, good hydration or different therapies for kidney protection to avoid CIN may be necessary for patients with renal impairment.

Bleedings

The Carillon procedure requires a venous access through the right IJV using a 9F sheath to allow the advancement of a multipurpose catheter (5 or 6F) to selectively cannulate the CS and an arterial access (usually radial with a 6F sheath) to perform a coronary angiogram to assess the relationship between the CS and the coronary three before and during the procedure. As in each percutaneous procedure access, site-related bleedings may occur. To reduce the bleeding risk, an echo-guided IJV puncture should be performed and any vitamin K antagonist oral anticoagulants must be discontinued 3 days before the procedure to achieve an INR between 1.5 and 1.7. In patients under treatment with novel anticoagulants, it is suggested to suspend the treatment 24–48 h before the procedure, depending on the molecule and the renal function of the patient.

Unlike other MV percutaneous repair procedures (i.e., MC or Cardioband), the Carillon™ procedure does not require transseptal access reducing the risks of interatrial septum puncture-related pericardial effusion or cardiac tamponade (**Figure 3**). Despite low, the risk of both major bleedings is still present during CS cannulation and guidewire/delivery system advancement within the CS. Perforation or dissection of the CS (3 cases over 48 patients enrolled in the AMADEUS trial (36) may have in the majority of cases a self-limiting course while in the minority may lead to pericardial effusion or cardiac tamponade) (**Figure 4**). In the latter cases, protamine should be quickly administered to reduce the ACT as much as possible (<200 s) and pericardial drainage should be emergently performed in case of unstable hemodynamic conditions. The possibility to continue the procedure is left, case by case at the operator's discretion according to the patient's hemodynamic stability and general clinical conditions. Complications during the cannulation of the CS are correlated with the learning curve and their rate is similar to that observed in early studies of cardiac resynchronization therapy where CS cannulation is needed (38).

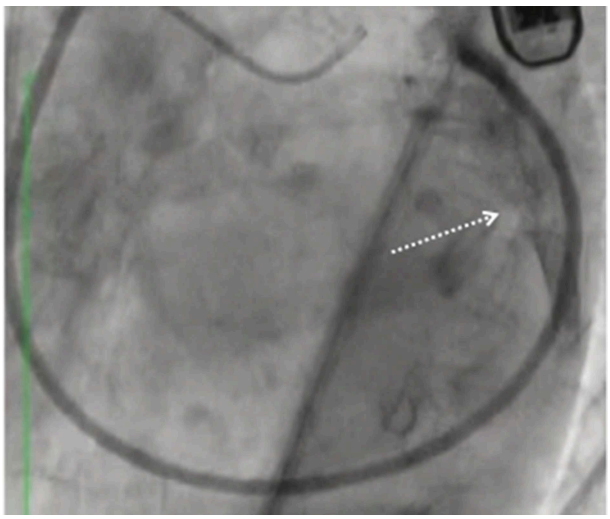

FIGURE 3 | Pericardial effusion (arrow) and cardiac tamponade following the Carillon device delivery system advancement outside the coronary sinus.

Extrinsic Coronary Artery Compression

Given the contiguity of the CS with the coronary arteries, especially the left circumflex artery (LCA), their compression could happen following device deployment and tensioning. A diagonal or ramus branch may have a trajectory between the CS and MA in 16% of patients (39). Special attention should be given to the LCA, which runs between the CS and the MA, in a high percentage, ranging between 64 and 80% of cases (40–42). The LCA may suffer frequently extrinsic compression due to this close relationship with the CS. Moreover, the LCA branches may be also potentially involved (43). If the Carillon™ device is in close relation with a coronary artery segment with a previously implanted stent, it's deployment should de aborted due to the potential compromise of the stent integrity.

A simultaneous CS venogram (left anterior oblique 30° projection) and coronary angiogram at the start of the procedure and coronary angiogram just before the release of the device are mandatories to assess eventual coronary artery extrinsic compression. In case of significant coronary narrowing due to indirect compression, the tension of the implanted device must be reduced and/or the Carillon™ system could be retrieved

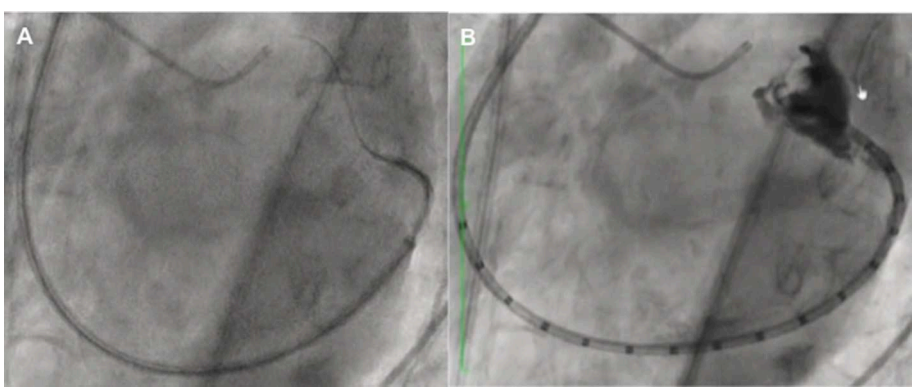

FIGURE 4 | Uncontrolled hydrophilic wire advancement **(A)** leading to coronary sinus perforation **(B)**.

through a specific capture system to be repositioned (44). In the case of persistent compression (despite tension reduction or device repositioning) associated with EKG modifications, the implantation procedure must be aborted (17% of cases reported in the TITAN II trial) (35).

Partial Device Dislodgment/Fracture

The first generation of the device suffered modifications (the shape of the anchors are twisted at the apex providing more rigidity) due to some reported cases of slippage of the distal anchor, which prevented the final release of the implant. One case of device fracture (not fatigue-related) was seen in the TITAN II trial in a patient in whom the device could not be recaptured, leaving a recaptured/redeployed, damaged proximal anchor in the middle of the great cardiac vein at the site of dynamic venous compression. The fracture was not associated with a clinical event (35).

Reduced Strength of the Metal

Another potential complication during Carillon™ implantation can be the reduced strength of the metal (nickel and tantalium composing the shaping ribbon between the anchors of the device), which can fail the device in terms of mitral regurgitation degree reduction. With the second generation of the device, used in the TITAN study (37), the number of cases with device failure was significantly reduced and the outcome was improved.

No complete device embolization/dislodgment, procedure-related infections, conduction abnormalities, or iatrogenic mitral stenosis were reported until now following Carillon™ implantation.

Mitralign™ System Device and Potential Complications

Mitralign (Mitralign, Tewksbury, Massachusetts) is a direct annuloplasty system that uses radiofrequency energy to penetrate sutures for two bident pledgets into the MA tissue posterior and anterior to the commissure (both, atrial and ventricular sides). By cinching the sutures, the MA becomes reduced. The procedure is performed under general anesthesia, guided by 2- and 3-dimensional TOE and fluoroscopy, it requires arterial femoral access, and 14F deflectable guiding catheter manipulation within the LV. The procedural steps were extensively described elsewhere (45) while the procedure aims to reduce the degree of functional MR in the symptomatic patient by the reduction of the MA dimension. Data from the first-in-man trial on 71 high-risk patients demonstrated positive results in terms of LV reverse remodeling, and clinical improvement during 6 months after treatment (46). The main procedural complications reported were cardiac tamponade and access site bleedings (46).

Pericardial tamponade occurred in 4 patients (8.0%) and was managed uneventfully with pericardiocentesis in all the cases with no need for emergency cardiac surgery. Three of the 4 tamponades were related to catheter manipulation within the LV. One of the tamponades led to the exclusion of LV end-diastolic diameter $r < 5.0$ cm while 2 of them were a function of the early learning curve and first-generation devices. Thus, the exclusion of LV end-diastolic diameter <5.0 cm and second-generation catheter systems have mitigated potential risks of tamponade.

Concerning arterial access, there were 6 (8.4%) bleeding complications reported. Three of the complications required transfusion and 3 did not. All were managed conservatively without the need for surgery or interventional repair/stent placement (46).

Cardioband™ Device

The Cardioband (Edwards Lifesciences, Irvine, CA) is a device designed to perform direct percutaneous annuloplasty (supra-annular fixation like in surgery) of symptomatic patients (NYHA II-IV) with dilated cardiomyopathy and moderate-severe functional MR (due to MA enlargement) by means of a half-ring implanted in the posterior MA, with beating heart, and under fluoroscopic and TOE guidance. Aim of this procedure is to reduce MR by annular reduction. The device and the procedure have been previously described elsewhere (47).

Briefly, the Cardioband implant is a polyester sleeve with radiopaque markers spaced 8 mm apart containing a pre-mounted contraction wire connected to an adjusting spool. The device is fixed *in situ* thanks to a series of helical stainless steel implantable anchors and is equipped with a system that allows adjustment of the degree of annular reduction to achieve a good result in terms of residual MR, without creating stenosis.

The procedure is performed under general anesthesia through venous femoral access and a 25F transseptal steerable sheath (47). Pre-procedural CT scan is mandatory to exclude patients with anatomical contraindications ("superficial" LCA, MA calcification, small left atrial chamber). Furthermore, a simulation of the entire procedure is carried out at the core lab using cardiac CT to plan the number of anchors that need to be released to cover from the anterior area of the lateral commissure toward the posterior area of the medial commissure of the posterior MA.

The optimal position of the transseptal puncture is also determined off-line by CT analyses for each patient and the puncture is echo-guided during the procedure. Encouraging clinical results on 60 patients at 1-year follow-up was recently published (48), even though several complications were described (46, 47).

Complications Following Direct Percutaneous Mitral Annuloplasty Using the Cardioband™ Device

Peri-Procedural Stroke

Cardioband implantation is a relatively long-procedure (total procedural time and device implantation time 201 ± 58 min and 175 ± 50 min, respectively) (48) and different materials (steerable sheath, anchors, band) are manipulated within the left atrium. On this basis, heparin administration is fundamental to maintain an ACT between 250 and 300 s to ensure adequate patient anticoagulation avoiding thrombo-embolic complications. Following implantation, no oral anticoagulation is needed and the dual antiplatelet therapy regimen is indicated according to prior cardiovascular events/procedures. Despite a careful

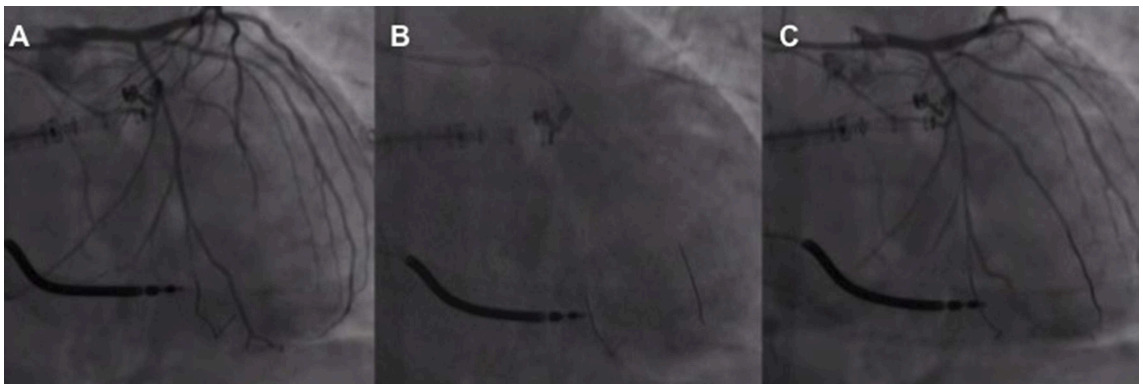

FIGURE 5 | First obtuse marginal narrowing associated with the slow flow **(A)** following implantation and release of the first Cardioband anchor managed with non-compliant balloon inflation **(B)** with narrowing resolution and flow restoration **(C)**.

intra/peri-procedural anticoagulation management, one immediate post-procedural, non-fatal ischemic stroke was reported in 1 over 60 patients while one fatal hemorrhagic stroke, few days after device implantation was described in a patient being treated by triple anticoagulant therapy (aspirin, ticagrelor, heparin, and vitamin K antagonist) because of a recently implanted coronary stent and atrial fibrillation (48).

Left Circumflex Artery Injury

LCA injury (obstruction or perforation) secondary to anchor placement was reported in 2 over 60 cases (48). This is a well-known complication of mitral valve surgery/intervention (**Figure 5**). Since then, the screening process for the Cardioband procedure has improved based on CT evaluation assessing the distance between the myocardial surface at the theoretical anchor releasing zone and the LCA. Furthermore, a procedural coronary angiography is recommended before inserting and releasing anchors, especially for the first anchors due to the proximity of the LCA to the MA near the lateral commissure. In the largest report of Cardioband treated patients, LCA injuries have been associated in one case with myocardial infarction while in the other with cardiac arrest due to ventricular rhythm disturbance. Both the events were successfully solved and the patients survived the events (48).

Transient LCA occlusion due to cinching-related coronary kinking despite avoiding injury by the anchor was also reported. Cinching reduction (from 4.5 to 3.5 cm) and stent implantation at the proximal LCA have been adopted as solutions to avoid LCA kinking resolving the acute ischemic myocardial damage (49).

Anchor Disengagement

This complication may lead to partial device detachment which might impact device efficacy with significant MR recurrence (47, 48) but any device migration, embolization nor intravascular hemolysis was reported associated with this phenomenon. Since anchors are delivered through the sleeve, if disengaged, they remain within the band and there is theoretically no risk of anchor migration or embolization. No late (more than 30 days) disengagements were reported even if one case of subacute (after 3 days) dehiscence across P2 with 5 anchors disengagement leading to MA laceration, severe MR recurrence and cardiogenic shock requiring Cardioband surgical explantation and left ventricular assist device positioning was recently described (50). Improper or insufficient anchor insertion and a prior shift in the manufacturing process were advocated as potential causes of all incidents of anchor disengagement.

Important improvements were performed to overcome this potential complication. Anchor length was increased from 4 to 6 mm, giving more stability and better anchoring within the myocardium. During cinching the lateral commissure area gives important support, and additional anchors were used to reinforcing this area. The improvement of the imaging techniques, using multiples views made the procedure safer, paying special attention during the pull test in the P2 area (second area at risk for disengagement). The device design was improved to avoid contraction failure, which also occurred early in the series.

As with other devices, the learning curve is important. Indeed, 9 of the 10 anchor disengagement (5 resulting in device inefficacy) occurred in the first 28 patients enrolled in the CE mark trial (47).

Training of both interventional cardiologists and echocardiographers is crucial to reduce this complication and to increase the device success rate [(48); **Figure 6**]. However, due to the risk of delayed (subacute) dehiscence close echocardiographic controls are of paramount importance at follow-up.

Conduction Disorders

Despite the proximity of the deployed ring to the atrioventricular (AV) conduction system, only one case of complete AV block has been reported until now (51). In particular, a late-onset (26 h after the procedure) Mobitz 2 AV block then evolved to complete AV block (in the following day), requiring definitive biventricular pacemaker (PM) was described in an 80-year-old patient with prohibitive surgical risk, treated with Cardioband implantation (17 anchors) for functional MR.

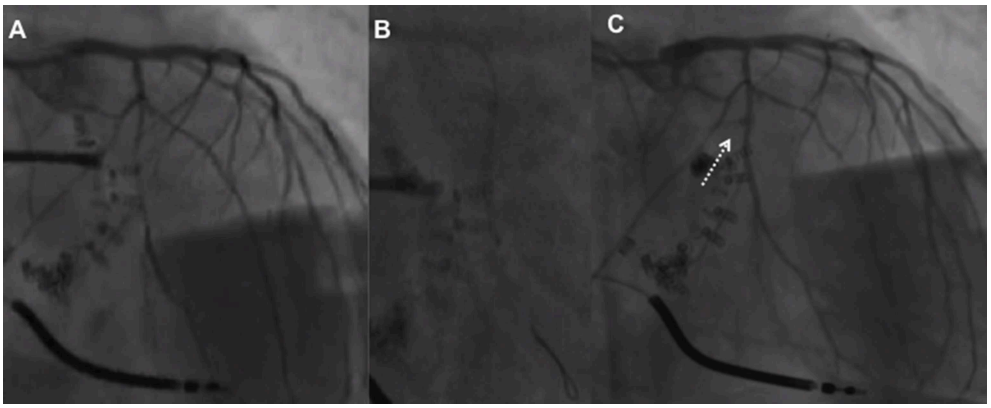

FIGURE 6 | Flow reduction on distal left circumflex **(A)** after the third anchor placement managed by balloon inflation **(B)** which caused anchor detachment with residual coronary-left atrial fistula (**C**, arrow) managed conservatively (covered stent did not advance through the left main toward the left circumflex) with the resolution at 1 month.

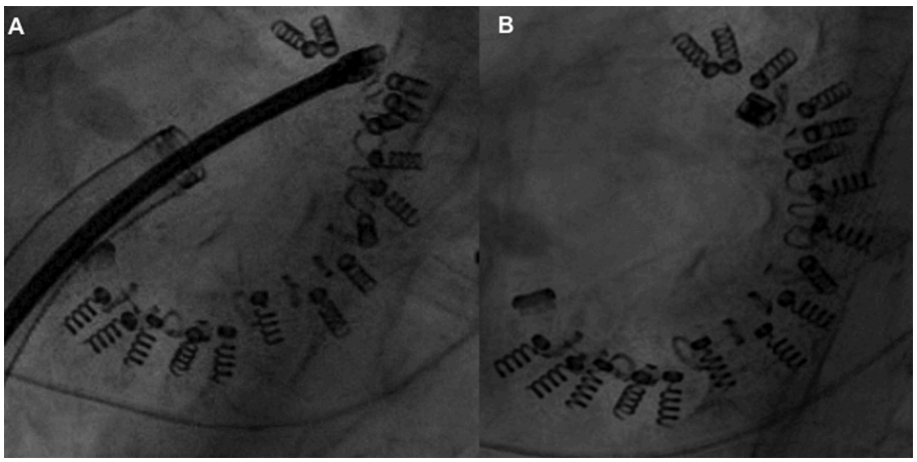

FIGURE 7 | (A,B) Guidewire rupture and implant contraction failure with loose of the cinching initially acquired.

The sub-acute AV block, without any electric disturbance during implantation or cinching is difficult to be explained while the late presentation might be related to the pressure exerted during heart contraction causing permanent damage around the screws where the conduction system is located.

Manipulation of the CS area during different transcatheter interventions may affect the AV conduction system, which is in the vicinity of the CS. Although just one case of late AV block was described, this event should not be generalized and considered as a frequent complication after Cardioband. Moreover, prolonged EKG monitoring after a similar procedure with CS area manipulation should be considered (51).

Acute Impairment of Left Ventricular Systolic Function

Similarly to other percutaneous mitral repair procedures performed in patients with functional MR (52), acute impairment of left ventricular (LV) systolic function (afterload mismatch) may occur even after Cardioband procedures (48). Although this phenomenon is usually transient (without long-term prognostic implications) and less frequent compared to surgical MV repair, inotropic drugs may be required to support the circulation. However, it is well-known that β-adrenergic agonists (i.e., dobutamine, adrenaline, and dopamine) may favor on the other hand myocardial ischemia, arrhythmias and increase mid-term mortality in patients with severe LV dysfunction (53).

In this setting, the administration of levosimendan 0.01 μg/kg/min before, during and after the procedure might help to reduce the risk of acute hemodynamic worsening following percutaneous functional MR correction (54).

Implant Contraction Failure

This complication may occur in the last phase of the procedure.

After the deployment of the last anchor and the removal of the implant delivery system (IDS), the size adjustment tool (SAT) is then inserted through the trans-septal steerable sheath (TSS), over the implant guidewire, until its distal end reaches the adjustment spool of the implant. After the SAT connection,

the implant is contracted by clockwise rotation of the adjustment roller (47). Adequate reduction of MR severity is assessed by TOE under beating heart conditions. When the appropriate implant size has been reached, the SAT is detached from the adjustment spool leaving the implant with the desired degree of contraction.

In the early experience, two cases of residual significant MR were described and related to the impossibility to contact the Cardioband after the implantation because of technical device failure (**Figure 7**). This device-related failure was solved with an iteration of the device after the first initial experience (10 patients treated) (47).

Contrast-Induced Nephropathy (CIN)

The Cardioband implantation procedure itself does not require the administration of contrast medium as anchors positioning is performed under 3D TOE guidance. However, several injections of contrast dye might be needed to assess the coronary artery anatomy and the relationship between the LCA and the first anchors implanted. Two cases of CIN (over 60 patients reported) after Cardioband implantation have been reported (48).

Therefore, considering that 75% of the patients treated had renal insufficiency before the procedure, good hydration or the use of other means to protect against CIN may be necessary case-by-case according to the clinical features of the patient.

Other Serious Adverse Events

Other events reported during (or after) Cardioband implantation were: 2 pericardial effusion (possibly related to procedure), 1 left femoral pseudoaneurysm (related to procedure), 1 bleeding complication (related to procedure), 1 upper limb hemiparesis, 1 gastrointestinal bleeding, 1 late mitral valve endocarditis (47, 48).

No complications (i.e., cardiac tamponade, iatrogenic atrial septal defects) directly related to the trans-septal puncture/access were reported.

CONCLUSIONS

Nowadays, patients with severe MR and high risk for surgery have the percutaneous option for mitral valve repair with a low risk of potential complications.

With all-new technologies, the team must be aware of the procedure, with the complications that may occur and how they can solve it.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Emerging Technologies for Percutaneous Mitral Valve Repair

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Mitral regurgitation (MR) is a common disease affecting more than 4 million people in the United States and the European Union. A significant number of percutaneous valves have been developed recently, specifically designed for the mitral anatomy, and with a promising evidence of good procedural and echocardiographic outcomes. However, even if transcatheter mitral valve replacement (TMVR) will have a role in the future of percutaneous treatment of both functional and degenerative mitral regurgitation, percutaneous mitral valve repair will always play a vital role in the treatment of MR because of the favorable safety profile and the fact that it respects the native anatomy. In this review, we will discuss the new emerging technologies under development to treat mitral regurgitation focusing on different devices that aim to target different components of the mitral anatomy.

Keywords: mitral regurgitation, heart failure, mitral valve, transcatheter mitral valve replacement, mitral annulus

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INTRODUCTION

Mitral regurgitation (MR) affects more than 4 million people in the United States and the European Union and its prevalence increases with age, reaching up to 1 in 10 adults aged 75 years or older (1, 2). Degenerative MR (DMR) accounts for approximately one-third of all MR cases (3). Today, surgical mitral valve repair (MVr) is a robust and effective procedure to correct MR, with years of clinical experience and validated evidence. However, surgical mitral intervention in high risk patients is still a challenging procedure, with 30-day mortality approaching 3.1% (4). Furthermore, the mortality rate is even higher in patients with functional mitral regurgitation (FMR), where a concomitant impairment of the left ventricular ejection fraction (LVEF) is often observed (5).

For these reasons, emerging low risk percutaneous strategies are needed to treat MR in both degenerative and functional anatomies, and to minimize the potential complications associated with open-heart surgery. Percutaneous MVr technologies are required to replicate surgical mitral valve reconstruction, without disrupting the normal valve and ventricular physiology. In this review, we will discuss the potential future role of percutaneous MVr, offering an overview on the emerging technologies that are currently under investigation.

IS THE FUTURE STILL REPAIR?

A variety of repair techniques (including mitral leaflet devices, implantation of neochords and percutaneous mitral annuloplasty) has been introduced since the first MitraClip procedure in

2003. However, in most of these cases, emerging technologies have been dismissed because of suboptimal pre-clinical results, complicated implants, and difficult reproducibility of their results. The development of transcatheter MVr systems is facing the following challenges:

1) The degree of MR reduction with percutaneous repair technologies is not fully predictable, and a complete resolution is rarely guaranteed.
2) Mitral valve anatomy is complex and different mechanisms can contribute to regurgitation. As a consequence, a single repair device addressing a single target will unlikely achieve optimal results. For example, a certain degree of mitral annular dilatation is always present in patients suffering from severe MR. Surgical MVr usually combines various types of leaflet-plasty with annular reduction in order to minimize the risk of progressive annular enlargement and MR recurrence (6). On the contrary, percutaneous MVr procedures are often based on a single repair technique and are consequently considered "incomplete." The lack of knowledge on the long-term outcomes in these circumstances gives rise to concerns about the durability of MR reduction. Isolated published case reports show the feasibility of simultaneous implantation of MitraClip (Abbott Laboratories, Abbott Park, IL) and Cardioband (Edwards Lifesciences Corp., Irvine, CA, USA) as well as "rescue" percutaneous annuloplasty to treat MR recurrence after Mitraclip (7, 8). However, these still remain anecdotal cases and more data are needed.
3) The mitral annulus is a highly dynamic, asymmetrical structure, with a saddle-shape conformation that poses difficulties in the positioning and sizing of these devices. Therefore, the development of percutaneous annuloplasty systems has to overcome major design obstacles due to the aforementioned complex mitral annular structure. A circular prosthetic ring runs the risk of not matching the asymmetrical anatomy of the native mitral valve annulus, thus increasing the tension between the device and the mitral structure. This limitation along with the method of fixation (screws) could translate into an increased risk of late device detachment, which has already been observed in the early cases of percutaneous mitral annuloplasty (9).
4) A certain proportion of mitral anatomies are not the ideal candidates for repair and sometimes TMVR can be an alternative treatment option. Nevertheless, calcific and rheumatic MR still represent important unmet needs in transcatheter mitral intervention that may be associated with suboptimal results, both for repair (increased risk of post-procedural gradients) and replacement (due to the increased risk of para-valvular leakage and left ventricular outflow tract obstruction).

Abbreviations: MVr, mitral valve repair; MR, mitral regurgitation; FMR, functional mitral regurgitation; DMR, degenerative mitral regurgitation; TMVR, transcatheter mitral valve replacement; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification.

The Advantages of Repair Over Replacement

Taking into consideration the aforementioned challenges, a significant number of percutaneous valves have been recently developed, specifically designed for the mitral anatomy, and with promising evidence of good procedural and echocardiographic outcomes. However, even if TMVR will have a definite role in the future of percutaneous treatment of both FMR and DMR, percutaneous MVr will always play a vital role in the treatment of MR due to the following:

1) ***Technical aspects:*** Transcatheter valves and percutaneous annuloplasty devices have to adapt to the mitral annulus that, conversely to the fibrous ring of the aortic valve, does not provide a rigid anchor for sealing. Moreover, the mitral annulus is posteriorly embedded in the junction of the left atrium and left ventricle, while the anterior portion consists of the aorto-mitral curtain, a dynamic structure with limited rigidity. This poses multiple challenges for securing a device and bares the risk of compression and interference with the aortic valve apparatus. Data from the preliminary experience of these devices demonstrates that the risk of complications like valve erosion, migration, malposition at 1-year follow-up is around 4% (10). These complications theoretically do not exist in the case of MVr.

   The close proximity of the left ventricular outflow tract (LVOT) places it at a higher risk for obstruction, especially with high-profile valves. In one study on the early experience with TMVR, the rate of acute LVOT obstruction was 8.2% with transcatheter mitral valve-in-ring (ViR) procedures, and 9.3% following TMVR in the presence of severe mitral annular calcification (MAC) (11, 12). Acute LVOT obstruction has a negative impact on both, procedural and post-procedural outcomes. A neo-LVOT area of <1.7 cm^2 is highly predictive of obstruction, and patients with this anatomy should be considered for MVr rather than replacement (13). LVOT obstruction is not a problem with percutaneous MVr, since the devices implemented for percutaneous mitral valve plasty are much smaller in size, and have a favorable profile that respects the mitral valve anatomy.

   Lastly, the anatomical position of the mitral valve apparatus can be easily reached through a transapical approach. However, in sick patients with low ejection fraction, the presence of apical scar, and thinning of the apical wall are deleterious, thus an alternative access would be preferable to minimize the risk of complications. A fully percutaneous transfemoral trans-septal venous approach would be desirable but, in comparison to MVr, it would imply larger iatrogenic interatrial defects and it would require a highly flexible delivery system to coaxially reach the mitral valve plane (14).
2) ***Durability:*** Although no long-term durability data exist for TMVR, we know from surgery that structural valve degeneration occurs more frequently in mitral bioprosthetic valves than in the aortic valves, and in younger individuals (15). From our clinical experience we also learned that patients undergoing TMVR are younger and have a longer

life expectancy compared to transcatheter aortic valve implantation (TAVI) patients. All these reasons raise the alarms regarding the long-term durability of these valves. Conversely, the devices used for MVr can potentially last for decades without a concrete risk of erosion or degeneration.

3) ***Device thrombosis:*** TMVR prostheses are potentially more prone to thrombosis due to the larger size, the high profile and the huge amount of "foreign" material of which they are made. Moreover, the atrial aspect of the mitral prostheses is exposed to low atrial pressures that can contribute to blood stasis, and subsequently to valve thrombosis. The early experience in 100 patients reported a device thrombosis rate of 6% at 1-year (16). Conversely, percutaneous MVr is more physiological as the implanted device is not as bulky as TMVR and the smaller surface area can mitigate the risk of device thrombosis.
4) ***Paravalvular Leak (PVL):*** Paravalvular leak (PVL) is a common complication of mitral valve replacement (15). Although most PVLs have unknown clinical significance, ∼3% of patients will have signs and symptoms of hemolysis, heart failure or a combination of the two (17). Significant PVL is relatively rare in cases of TMVR in non-calcified mitral annuli, while in cases of TMVR in MAC, the rate of moderate to severe PVL at 30 days can reach up to 13.8% (18). In MVr the risk of PVL leading to hemolysis is theoretically non-existent.

TRANSCATHETER MITRAL VALVE REPAIR: WHAT CAN WE EXPECT FROM THE FUTURE

MR is the most frequent valve disease in the population and it's prevalence increases with age (19). Open-heart surgery is considered the gold standard for the treatment of severe MR, with excellent outcomes achievable in most patients. However, more than 50% of patients with severe MR are excluded from surgery due to an increased perioperative risk related to comorbidities (20). In particular, patients with FMR, have a high perioperative mortality ranging between 6.6 and 11.4% (21). Whereas, the use of an effective percutaneous MVr system can result in a lower perioperative risk with similar clinical benefits compared to surgery at follow-up. Lastly, we hypothesize that the number of future percutaneous mitral valve procedures will be influenced by the following factors:

- The results of the recently published COAPT and MITRA-FR trials have demonstrated that moderate to severe FMR has a clear clinical impact on prognosis, and a successful treatment of FMR with the MitraClip system in selected patients can significantly reduce the rate of rehospitalization, and all-cause mortality at 2-years follow-up (22, 23).
- The prevalence of heart failure will increase by ∼50% between 2012 and 2030, resulting in more than 8 million people older than 18 years-old with heart failure. This daunting future reflects the increased prevalence of heart failure as the population ages, and the improved survival of patients with acute myocardial infarction and heart failure itself. In parallel, this progressive increase of heart failure prevalence will translate into a higher rate of MR. Hence, percutaneous treatments to fix MR will be necessary given the high surgical risk profile of this population (24).
- In the near future, the threshold for percutaneous treatment of multiple valvular diseases will be lowered. TAVI has already been demonstrated to be non-inferior or even superior to surgical aortic valve replacement in low risk patients. Percutaneous treatment of concomitant significant MR in this population will be considered a desirable option (25, 26).
- The armamentarium of devices for the treatment of MR will expand, offering a wide number of percutaneous options that will be able to accommodate a larger variety of anatomies.

EMERGING DEVICES

A wide number of MVr systems are currently under development (**Figure 1**). The following section provides a brief overview of these devices and of the ongoing clinical studies on transcatheter mitral valve repair (**Table 1**).

Millipede IRIS

The Millipede IRIS is a complete, semi-rigid annuloplasty ring (Boston Scientific, Marlborough, Massachusetts). The system is composed of eight stainless-steel anchors that are connected by sliding collars and nitinol frames, located in the upper position of the device. Each anchor can be independently and reversibly fixed to the mitral tissue in order to customize the size and the site of anchoring. The Millipede IRIS has been implanted both surgically, using a trans-atrial approach, and percutaneously, with a 24 French steerable catheter delivered trans-septally. The first clinical experience with IRIS included seven patients: four were treated using a conventional surgical approach, while three patients were treated percutaneously. The percutaneous implant of the device was monitored under fluoroscopy and using both transesophageal and intracardial ultrasound (ICE) monitoring. The adjunctive use of ICE allowed a direct visualization of the mitral annulus and a detailed placement of the IRIS anchors. All the iatrogenic atrial septal defects were closed with a 10 mm Amplatzer septal occluders (Abbott, Santa Clara, CA). The authors reported no major adverse events and a procedural success obtained in all the cases. The implant resulted in a significant reduction in the septo-lateral diameter (from 38.0 ± 4.1 to 25.9 ± 4.9 mm), and in a significant reverse remodeling of the left ventricle, with a decrease in diastolic left ventricular volumes from 182.4 ± 54.3 to 115.3 ± 98.8 mL at 30 days. Every patient demonstrated reduction of MR, with all patients showing a decline from a baseline of 3 or 4+ MR to 0 or 1+ MR at 30 days (27). One of the patients who received a surgical implantation of the IRIS Millipede in combination with an A2/P2 Alfieri leaflet repair, performed in standard fashion, experienced a relapse of MR at 12 months follow-up due to a newly ruptured chordae tendineae, just lateral to the original Alfieri stitch. In this patient, an adjunctive MitraClip was placed with a residual trivial MR (28).

The Annular Reshaping of the Mitral Valve for MR Using the Millipede IRIS System (NCT02607527) is an early

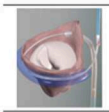
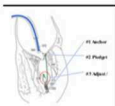
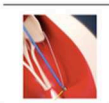
DEVICE	NAME	DESCRIPTION	CURRENT EXPERIENCE
	**Millipede IRIS** (Boston Scientific, Marlborough, Massachusetts)	- Antegrade direct annuloplasty system - Both surgical and percutaneous implantation through interatrial septum - Complete nitinol ring - Repositionable and retrievable	7 patients implanted with 100% procedural success
	**MVRx ARTO** (Ample Medical Inc; Foster City, CA)	- Incomplete indirect annuloplasty system - Composed of 2 magnets placed in the great cardiac vein and in the left atrium - To reduce the antero-posterior dimension of the mitral annulus	Mitral Valve Repair Clinical Trial (MAVERIC)
	**Valcare Amend** (Valcare Medical; Israel)	- Complete annuloplasty system - Delivered through transeptal or transapical approach - 3 sizes available	14 patients treated, alone or in combination with other devices
	**Accucinch GDS** (Ancora Heart, Inc., Santa Clara, CA)	- Retrograde direct annuloplasty system targeting the sub-annular LV myocardium - Double mechanism: reduction of the septal-free wall dimension and of the LV volume	16 patients treated
	**Mitral Loop Cerclage** (Tau-PNU Medical Co, Ltd, Pusan, Korea)	- Indirect annuloplasty system - Transjugular and transfemoral access	5 patients treated
	**Pipeline** (Gore, Flagstaff, Arizona, USA)	- Chordal system - Transfemoral/transeptal access	Pre-clinical investigation on ovine models
	**Mitral Bridge** (Heart Repair Technologies, Inc.)	- Transannular mitral bridge - Both percutaneous access and thoracotomy	- 34 patients surgically implanted - Pre-clinical investigation on transeptal device
	**ChordArt** (CoreMedic AG, Biel, Switzerland)	- Chordal repair technology - Both through the atrial septum or anterogradely	- Pre-clinical studies in 5 sheeps and 5 pigs - 1 human compassionate use
	**CardioMech** (CardioMech AS, Norway)	- Chordal repair technology - Transfemoral venous access/transeptal puncture - Removable and repositionable anchors on LV	Research and development phase
	**MitraClamp** (Heartworks LLC)	- Sutureless posterior leaflet plication device - Transcatheter/transeptal approach	Ex-vivo study on pig hearts
	**NeoChord** (Neochord, Inc., Minnetonka, Minnesota)	- Chordal repair technology - Transapical access - Transeptal access under development	- More than 1000 patients treated; - Largest cohort analyzed (n = 213) in a multicenter European registry - 1 case published reproducing edge-to-edge [40]
	**Mitral Butterfly** (Angel Valve, Wien, Austria)	- For the treatment of the posterior MV leaflet prolapse - Both anterogradely and retrogradely	- The clinical development program planned to start in 2019 with a pre-clinical phase in sheeps - The first in man procedure planned in 2021
	**Polares** (Palo Alto, California, United States)	- Hemi-replacement system of the posterior leaflet - Both for FMR and DMR	Ovine models only
	**MitraMaze** (Coramaze technologies, Hilden, Germany)	- Coaptation enhancer device - Transfemoral approach	Ovine models only
	**Sutra** (Dura Biotech)	- Hemi-valve to treat isolated defects of the posterior leaflet - Enhance the systolic coaptation with the native leaflet - Crescent shaped stent frame - Annular anchoring	Only pre-clinical studies on animal models

FIGURE 1 | List of the emerging repair technologies available for mitral valve.

feasibility clinical trial with the aim of enrolling 50 patients with symptomatic severe MR treated percutaneously with the IRIS device.

MVRx ARTO

The MVRx ARTO (Ample Medical Inc.; Foster City, CA) is an incomplete and indirect annuloplasty system. The system is composed of two magnets (MagneCath) that are placed in the great cardiac vein and in the left atrium at the level of A2/P2 scallops. Once the two magnets are close to each-other, a specific guidewire is passed through the two MagneCath from the great cardiac vein to the left atrium, aligning the two catheters. After using an exchange catheter, the loop guidewire is placed across left atrium. This guidewire directs the placement of the great cardiac vein anchor (T-bar) and septal anchor. Once in place, an appropriate tension is applied to reduce the antero-posterior dimension of the mitral annulus. The results of the Mitral Valve Repair Clinical Trial (MAVERIC) have been published, where the authors reported the 30-days outcome of 11 patients that were treated with the MVRx 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. One patient had pericardial effusion, and one asymptomatic device dislodgment were reported at 30-days, with no other major adverse events (29). To evaluate the safety and efficacy of this system in patients with MR secondary to annular dilatation, the MAVERIC EU (NCT02302872) and the MAVERIC US (NCT03311295) clinical trials are recruiting 45 and 15 patients in Europe and the United States, respectively. A total of 45 patients have been recruited in both trials with 1-year echocardiographic follow-up available in 35 patients. The authors report a significant reduction of the mitral annular dimensions from 41.4 to 35.3 mm, sustained at 1-year, with a freedom from residual moderate MR obtained in 92% of patients. At the follow-up, 11.4% of patients died for cardiovascular reasons, with no device malfunctioning reported (30).

Valcare Amend

Valcare Amend system (Valcare Medical; Israel) is a complete, semi-rigid D-shaped percutaneous annuloplasty system. The ring is available in three sizes to fit a wide range of mitral annular dimensions (29–50 mm). Once in place, the ring is delivered starting from the posterior part of the annulus. The annuloplasty ring is designed to be delivered through a transseptal or a trans-apical approach. This annuloplasty system has been tested in different scenarios and in combination with other therapies. A total of 14 patients have been treated in the first clinical experience: eight patients with FMR have received Valcare Amend as a single therapy. Whereas, two patients with DMR have received Valcare Amend as a single therapy. In another four patients, the system has been utilized in combination with MitraClip (three patients) and with NeoChord (one patient). The implant resulted in a 74% reduction of the jet area and in a 20% reduction in the antero-posterior diameter (31). In a single case, an unplanned MitraClip was implanted to treat significant residual mitral regurgitation. The Mitral Valve Repair

TABLE 1 | Ongoing trials for each mitral valve repair system.

Device name	Ongoing trials	Description
Millipede IRIS	**NCT02607527:** The annular reshaping of the mitral valve for MR using the millipede IRIS system Recruiting	Enrollment period: January 2017/2020 Multicenter Single group assignment Estimated 50 patients Primary endpoint: acute safety Secondary endpoint: efficacy
MVRx ARTO	**NCT02302872** (MAVERIC EU): Treatment of heart failure and associated functional mitral valve regurgitation Recruiting	Enrollment period: October 2013/May 2020 Single group assignment Estimated 45 patients Primary endpoints: MAE at 30-days, MR grade and change from baseline at 30-days, device technical success
	NCT03311295 (MAVERIC US): MitrAl valve repair clinical trial—United States Recruiting	Enrollment period: April 2018/2024 Single group assignment Estimated 15 patients Primary endpoints: safety at 30-days, efficacy
Valcare amend	**NCT02602613** (AMENDTM trial): mitral valve repair system, annuloplasty ring applied in a transcatheter method Recruiting	Enrollment period: December 2015/2018 Multicenter Single group assignment 40 patients Primary endpoints: safety at 30-days, device technical success
Accucinch GDS	**NCT03183895** (CorCinch-EU Study): safety and performance evaluation of the accucinch ventricular repair system for functional mitral regurgitation due to dilated ischemic or non-ischemic cardiomyopathy Not yet recruiting	Enrollment period: February 2019/January 2023 Multicenter Single group assignment Estimated 132 patients Primary endpoint: safety at 30-days Secondary endpoints: technical success, structural performance, freedom from re-hospitalizations or re-interventions, improvement in status
	NCT03560167 (CorCinch-PMVI Study): an early feasibility study of the accucinch ventricular repair system in patients with prior mitral valve intervention (PMVI) and recurrent mitral regurgitation Recruiting	Enrollment period: June 2018/September 2024 Multicenter Single group assignment Estimated 15 patients Primary endpoint: device-related or procedure-related MAE
Mitral loop cerclage	**NCT03453853** (AFRICA Study): atrial functional mitral regurgitation response in mitral loop cerclage annuloplasty Recruiting	Enrollment period: April 2018/March 2020 Multicenter Single group assignment Estimated 5 patients Primary endpoint: change of mitral regurgitation severity/mitral annulus geometry at 30-days, safety at 30-days
Mitral bridge	**NCT03511716**: HRT observational study of a mitral bridge in patients with moderate to severe mitral valve regurgitation to evaluate device safety and performance Active, not recruiting	Enrollment period: February 2014/July 2020 Multicenter Observational 34 patients Primary endpoint: freedom from subsequent open mitral valve repair or replacement
ChordArt	**NCT03581656** (CHAGALL): ChordArt System Study for the Treatment of Mitral Regurgitation Due to Leaflet Prolapse or Flail Recruiting	Enrollment period: March 2018/July 2020 Multicenter Single group assignment Estimated 40 patients Primary endpoint: all cause mortality/MAE at 30-days Secondary endpoint: technical success, device performance at 30-days
NeoChord	**NCT02803957** (ReChord): Randomized Trial of the NeoChord™ DS1000™ System Versus Open Surgical Repair Recruiting	Enrollment period: November 2016/July2025 Multicenter Randomized trial Estimated 585 patients Primary endpoints: freedom from MAE/ grade II, III or IV MR, mitral valve replacement or mitral valve reintervention at 30-days

MAE, major adverse event; MR, mitral regurgitation; NYHA, New York Heart Association; 6MWT, 6-min walk test; KCCQ-QoL, Kansas City Cardiomyopathy Questionnaire for Quality of Life; LV, left ventricle.

System, Annuloplasty Ring Applied in a Transcatheter Method (AMENDTM trial, NCT02602613) is currently recruiting with a target sample size of 40 patients to evaluate the efficacy and safety of the device.

Accucinch GDS

The Accucinch GDS device (Ancora Heart, Inc., Santa Clara, CA) is a direct ventriculoplasty system targeting the sub-annular left ventricular myocardium. The system includes a delivery catheter, a modular guide tunnel (MGT), an anchor delivery catheter and 12–16 nitinol anchors, connected by an ultra-high molecular weight polyethylene cinch cable to exercise tension over them. Proximal and distal anchors are interspaced with nitinol force distribution members. The system is implanted retrogradely using an 18 French guiding catheter delivered through the aortic valve. The Accucinch GDS implant can be customized according to the sub-annular space anatomy and to the thickness of the left ventricular wall. Anchors are delivered from commissure to commissure through an arch beneath the posterior leaflet of the MV in the ventricular free wall. Once the system has reached the sub-annular space, the MGT is oriented in direction of the myocardium and gradually withdrawn to facilitate anchor delivery through an inner tunnel with a single window. Once all the anchors have been released, tension is applied to the cinch cable using the cinch and lock catheter. A cut catheter is then utilized to cut the cinch cable before removing the MGT and the guide catheter (32). Thanks to the implantation site, the Accucinch GDS device acts with a double mechanism; it reduces the septal-free wall dimension, drawing the papillary muscles and the mitral leaflets in close proximity, and reduces the left ventricle volume without extracting muscle. Compared to the first implants, the latest version of the device is more flexible. Moreover, to achieve a greater volumetric reduction, the target zone now includes a wider part of left ventricular free wall. The Accucinch GDS has been attempted in 16 patients with two failures due to anatomical constraints and impossibility to achieve an adequate position of the delivery catheter. Among 14 successful implants, one procedure was complicated by pericardial effusion and stroke, that lead to the patient's demise. The 6 month echocardiographic data showed a significant reduction of the mitral regurgitant volume (from 60 to 37 ml) together with a sustained reduction of the left ventricular end-systolic volume (from 119 to 72 ml), with a continuous trend toward a progressive reverse remodeling of the left ventricle. The efficacy and safety of the device is under investigation in different scenarios (33). TheCorCinch-EU Study (NCT03183895) is an international multicenter, non-randomized, prospective safety study, designed to evaluate the AccuCinch Ventricular Repair System for the treatment of heart failure, with or without FMR due to dilated ischemic or non-ischemic cardiomyopathy. The Early Feasibility Study of the AccuCinch Ventricular Repair System in Patients With Prior Mitral Valve Intervention (PMVI) and Recurrent Mitral Regurgitation (The CorCinch-PMVI Study, NCT03560167) is actively recruiting, with target sample size of 15 patients with recurrent MR after failure of the previous valve intervention.

Mitral Loop Cerclage

The Transmural System Transcatheter Mitral Cerclage Annuloplasty (Tau-PNU Medical Co. Ltd., Pusan, Korea) is an indirect annuloplasty system composed of a stainless steel tension element with a coronary artery protection system. The two extremities of the tension element are connected using a bridge device that extends to the left subclavian vein. An adjustable extravascular lock is fixed subcutaneously in the subclavicular fossa and has the function to connect the tension element and the bridge, thus allowing a modulation of the tension under echocardiographic monitoring (34).

The procedure is performed using both the transjugular and transfemoral approach. Once the coronary sinus has been engaged, a pressurized venogram is performed to identify a perforator vein suitable for the intervention. A guidewire is then advanced in the perforator vein and externalized into the right ventricular outflow tract, passing through the interventricular septum. The externalized guidewire is then snared and pulled back into the inferior vein cava. The guidewire is subsequently exchanged with the Mitral Loop Tension device that is deployed with a protection device, to prevent the extrinsic compression of the circumflex artery. Once the tension device is *in situ*, the bifid coronary sinus tricuspid valve bridge is placed to prevent any damage of the septal tricuspid leaflet and of the conduction system. The first in human experience with the mitral loop cerclage annuloplasty was successful in 4 of 5 attempts. The mitral regurgitant volume and the septo-lateral mitral annular diameter were significantly reduced at 6 months (54 $\pm$ 8–18.5 $\pm$ 4.1 ml and 41.5–34.2 mm, respectively). The implantation of the mitral Cerclage also lead to a reduction of the left ventricular end diastolic volume (140 $\pm$ 62.5–102.6 $\pm$ 35.7 ml) (35). The Atrial Functional Mitral Regurgitation Response In Mitral Loop Cerclage Annuloplasty (AFRICA Study, NCT03453853) is a prospective, single-center, open label, feasibility study to assess the safety and efficacy of the Mitral Loop Cerclage Annuloplasty in treating FMR associated with heart failure and atrial fibrillation.

Pipeline

The Pipeline system (Gore, Flagstaff, Arizona, USA) is a newly developed system that targets the sub-annular apparatus, and acts as a chordal system that can be implanted using a transfemoral trans-septal approach. Once the delivery catheter reaches the left ventricle, a ventricular anchor is deployed from the catheter and fixed to the free wall, leaving a ventricular suture attached to the ventricular anchor. A leaflet pledget is deployed to secure the mitral valve leaflet to the ventricular anchor. The leaflet suture is secured to the ventricular anchor to limit the excursion the leaflet. This technology is currently under pre-clinical investigation with mid-term ovine models showing the feasibility of the procedure.

Mitral Bridge

Mitral Bridge (Heart Repair Technologies, Morgan Hill, CA, USA) is a newly developed technology that consists in a curvilinear nitinol band covered by a silicone overmold with velour pads at either extremity. The Mitral Bridge is positioned transversely across the mitral valve, linking the anterior and the

posterior leaflets at the level of A2-P2 segments, thus reducing the antero-posterior annular dimensions. A delivery handle, preattached to the implant, assists in positioning the bridge on the annulus with the curvature facing the ventricular cavity. Five septal-laterally oriented sizes of the mitral bridge (22, 24, 26, 28, and 30 mm) are available. The initial experience included 34 patients enrolled in the observational study of the Heart Repair Technologies Mitral Bridge in Treating Mitral Valve Regurgitation (NCT03511716), who received a surgical implant of the Mitral Bridge. At 2 years, no strokes or device-related adverse events were noted, and the MR was reduced from 3.32 ± 0.47 to 0.50 ± 0.83 ($P < 0.001$), with <1+ MR in 33/34 patients (including four reinterventions for periprosthetic recurrent MR ≥3 without mitral bridge explants or conventional mitral repair or replacement). At 2 years, the mean mitral gradient was 2.15 ± 0.82 mmHg, and the mitral annular septo-lateral dimension decreased from 40.4 ± 2.91 to 28.9 ± 1.55 mm (36).

ChordArt

The ChordArt *(CoreMedic AG, Biel, Switzerland)* is a fully percutaneous transcatheter mitral chordae implantation system, which can be delivered through the transtrially or transfemorally via the trans-septal approach. ChordArt uses a dedicated delivery catheter that grasps the mitral leaflet in the target area that needs to be treated. Once grasped, the delivery system is passed through the punctured leaflet until it reaches the papillary muscle. Once at the level of the papillary muscle, an anchor located at the distal tip of the catheter is fixed into the muscle. After this maneuver, the delivery system is retrieved leaving a suture that connects the grasped leaflet and the subvalvular apparatus. Pre-clinical studies have evaluated the safety and the efficacy of the system, surgically implanted in the beating heart of five sheep with acute chordal rupture; all procedures were successful and all of the five animal models were alive at 6 months follow-up, with no evidence of disruption or malfunction of the device. The ChordArt system has been subsequently implanted also in five pigs with acute mitral valve chordal rupture. The device has been implanted under fluoroscopy and echocardiographic guidance using left thoracotomy, with direct access through the left atrium on a beating heart. After the positive first in human experience for compassionate use, the device performance and the technical efficacy of ChordArt is currently under investigation in the ChordArt System for Mitral Regurgitation trial (CHAGALL, NCT03581656) with the planned enrollment of 40 patients suffering from a flail or prolapsed mitral valve leaflet (37).

CardioMech

CardioMech (CardioMech AS, Norway) is a transcatheter mitral valve chordal repair technology designed for the treatment of DMR due to prolapsed or flail leaflets. It is still in the research and developmental phase. It requires a transfemoral venous access and a transseptal puncture to reach the left atrium. The device is advanced through a 24Fr steerable delivery catheter to grip the prolapsing leaflet, then the new chordae is attached from the leaflet to the ventricular wall, where an anchor fixes it. Anchors are removable and repositionable. Studies to assess safety and feasibility are needed.

MitraClamp

MitraClamp *(Heartworks LLC)* is a new sutureless leaflet plication device designed for treating patients with mitral leaflet prolapse through a transcatheter approach. The U-shape arms are able to rotate around a common axis. Following leaflet grasping, leaflet plication is performed by rotating the two arms in two opposite ways. Pre-clinical study on the application of the MitraClamp in six fresh pig hearts demonstrated a dramatic reduction of the regurgitant volume during hydrodynamic tests. Device anchorage to leaflets was also found to be stable after device locking (38).

Neochord

The NeoChord Artificial Chordae Delivery System (Neochord, Inc., Minnetonka, Minnesota) is a transcatheter MVr technology performed through a transapical access (a transseptal access system is still under development). Under general anesthesia and transesophageal echo guidance, it allows the placement of expanded polytetrafluoroethylene (e-PTFE) sutures as replacement neochordae on a beating heart, without the need for cardiopulmonary bypass (39).

A relatively short learning curve is needed to achieve expertise in performing the NeoChord procedure safely (40). This contributed to the successful European experience and to the diffusion of the procedure so that, since its first application, more than 1,000 patients have been treated (41, 42). As for conventional surgery, the ideal candidates for NeoChord implantation are patients with isolated central posterior leaflet prolapse or flail, and patients with posterior multi-segment involvement. On the contrary, treating more complex lesions, such as those involving the anterior leaflet and paracommissural or calcified leaflets, has worse outcomes (43). Another predictor of success after NeoChord implantation is the Leaflet-to-Annulus Index (LAI), which is the ratio between the sum of the anterior leaflet length and the posterior leaflet length over the antero-posterior length. LAI values of ≤1.35, 1.30, and 1.25 are a positive prognostic predictor of residual regurgitation at 3, 6 months, and 1 year, respectively (44). According to these measurements, it is estimated that ∼25–30% of patients presenting with DMR can be effectively treated with the NeoChord procedure (40). To expand its application, one possibility is the synergic combination of this device with other transcatheter MVr systems, mimicking what already currently occurs with surgery. Otherwise, the group of Colli described another interesting application of the technique, as they reproduced the edge-to-edge intervention directly through transapical neochordal implantation with satisfactory results (45).

A currently ongoing multicenter, randomized trial (NCT02803957) comparing the NeoChord procedure with conventional surgical MVr in the United States will help provide further insights on the procedure.

Mitral Butterfly

The mitral Butterfly system (Angel Valve, Wien, Austria) aims to reproduce the butterfly repair technique for the treatment of the posterior MV leaflet prolapse. The butterfly repair consists of the combination of a triangular resection from the prolapsing

edge, with a reverse triangular resection to the annulus to remove redundancy (46). The Butterfly system consists of a nitinol stent with PTFE yarns and a swing arm that mimics an artificial papillary muscle. The implant can be performed both anterogradely and retrogradely using a steerable catheter. Once released, the Butterfly system contains the prolapsing posterior segment through the PTFE yarns; the position is stabilized thanks to the swing arm. The clinical development program (cOntaining prolapsing Segments to Correct mitral Regurgitation–OSCAR) is planned to start in 2019, and contemplate a first pre-clinical phase in sheep with the first in man procedure is planned in 2021 (47).

Polares

The Polares (Palo Alto, CA, USA) solution is a new concept in the vast armamentarium of mitral valve transcatheter technologies, it is a halfway between repair and replacement. It consists of the implantation of a posterior ePTFE neoleaflet to restore coaptation with the valve's native anterior leaflet. The development of this technology still needs to undergo clinical testing. To this date, implantation has been only performed in animal models.

MitraMaze

The MitraMaze system (Coramaze Technologies, Hilden, Germany) is a coaptation enhancer device composed of a flexible spacer, a nitinol crown and a customized delivery catheter system, which is specifically designed for the transfemoral approach. Upon release on site in the beating heart, the self-expanding implant design allows for an atraumatic anchoring in the left atrium, without the need to include adjacent myocardial tissue structures. A nitinol crown is left in the atrium and the spacer can be filled to reduce the coaptation gap between the mitral leaflets. In ovine models, the MitraMaze has demonstrated a significant reduction of the regurgitant volume (48).

Sutra

The Sutra (Dura Biotech) hemi-valve has been studied to specifically treat MR secondary to an isolated defect of the posterior mitral valve leaflet. The hemi-valve is composed of a tri-leaflet valve mounted on a crescent shaped stent frame. The hemi-valve is designed to enhance the systolic coaptation with the native leaflets, thus reducing the regurgitation. The hemi-valve is fixed to the posterior annulus through anchors that can be adjusted, thus allowing the possibility to cinch the native valve annulus. The first generation device has been surgically implanted in animals due to the lack of an anchoring system. However, the latest version of the device has been implanted in animals using the anchoring system. The device has demonstrated good safety and efficacy in reducing the regurgitant volume under hydrostatic testing (49).

CONCLUSIONS

Percutaneous MVr is a rapidly growing field, with several devices at different stages of development. Due to their capacity to preserve the complex inner anatomy of the mitral valve, these repair systems will have an important role in the treatment of MR. Large clinical cohort studies will help identify the right patient population that would benefit the most from transcatheter MVr. This breakthrough of new repair devices will enlarge the percutaneous armamentarium of MVr, offering a wide possibility of treatments customizable to specific anatomical features.

AUTHOR CONTRIBUTIONS

AM, ALar, FGi, and FGa produced a first draft of the manuscript. FK, ALad, and LT did a review of the literature. AC and ALat reviewed the article and gave their intellectual contribution to the manuscript.

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REVIEW
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Direct Percutaneous Mitral Annuloplasty in Patients With Functional Mitral Regurgitation: When and How

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Mitral regurgitation (MR) is a frequent valvular disease among patients deemed too high risk for surgery. Echocardiography along with CT is the primary diagnostic tool for MR and offers a comprehensive 3D assessment in patient selection and screening for the optimal treatment method. The direct percutaneous mitral annuloplasty addresses the underlying mechanisms of functional MR with a less invasive, catheter-based approach. The here-described techniques proved a sufficient safety profile, delivered significant MR reduction in most of the cases, and were associated with a notable improvement of symptoms. Although long-term outcome assessment is needed to support these early reports, the percutaneous mitral annuloplasty is likely to set a new standard of treatment in the forthcoming future.

Keywords: direct percutaneous annuloplasty, mitral annuloplasty, mitral regurgitation, transcatheter valve repair, mitral valve interventions, mitral valve imaging, patient selection, mitral annulus

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INTRODUCTION

Mitral regurgitation (MR) is the most frequent valve disease in developed countries (1). Referred to as secondary or as functional mitral regurgitation (FMR), it is caused by sustained left ventricle injury in the course of myocardial infarction or certain forms of cardiomyopathy, leading to left ventricle remodeling. That may result in the displacement of the papillary muscles and mitral annulus (MA) dilatation, yet the leaflet structure remains usually intact (2). Patients presenting FMR procure an unfavorable prognosis, resulting in over two-fold higher mortality when compared to primary MR and extremely high risk of heart failure (HF rate at 5 years, 78%) (3, 4).

Building on the years of experience with mitral valve replacement and repair procedures, together with a desire for a less invasive approach, multiple percutaneous technologies have emerged as a feasible and convenient therapeutic option for patients with MR. They can be classified depending on the anatomical and pathophysiological grounds: the indirect and direct annuloplasty, left ventricle (LV) remodeling devices, and leaflet and chordal repair procedures. This review aims to summarize current principles for patient selection and pre-procedural planning for direct transcatheter annuloplasty followed by the procedural know-how.

MITRAL VALVE ANNULUS STRUCTURE AND FUNCTION

The mitral valve complex consists of valvular (annulus, commissures, leaflets) and tension (papillary muscles, chordae tendineae) components. MA is the functional component of the valve

characterized by a non-planar, saddle-shape frame, believed to be involved in reducing stress on the valve elements during systole (**Figure 1**) (4). For interventional purposes, the annulus is regarded as the area of the attachment of the valve leaflets to the atrial part of the surrounding heart tissue. The anterior part consists of 1/3 of the valve circumference and incorporates a fibrous thick tissue, supported at each side of the base of the leaflet by the left (anterolateral) and right posteromedial fibrous trigones (5). Of more importance, the MA's three-dimensional geometry varies through the cardiac cycle. The standard correlation between the septolateral (antero-posterior) and transverse (inter-commissural) diameters of the MA is measured during systole and typically comes close to 3:4 (**Figure 2**). This can differ among patients with chronic MR, specifically when the leaflet coaptation is lost, even in the non-prolapsing segments (6).

Comprehensive assessment of MA still pose a challenge since different methods and settings have been used to establish the cutoff value. Since the 3D shape of MV annulus is other than simple, only a thorough examination is believed to be sufficient in clinical practice. The current cutoff for annular dilatation is based on transesophageal measurements of the end-diastolic antero-posterior MA diameter derived from a small group of 49 patients referred to MV surgery. This value is regarded as 35 mm and is still the most widely used in intraoperative setting (7).

In the non-surgical setting, the largest population-based echocardiographic dataset available to date is that of Dwivedi et al. This study was conceived specifically to determine standard mitral and tricuspid annulus dimensions with the use of 2D TTE. Gender-specific mean diameters of MA were 3.44 cm in males and 3.11 cm in females at end-systole and 3.15 cm in males and 2.83 cm in females at end-diastole. Interestingly, MA reduction in systolic phase was found to be up to 25% (8).

Some pivotal structures are closely located to the MA and should always be thoughtfully considered during all annuloplasty procedures: (a) the circumflex artery, which runs parallel to MV plane; (b) the coronary sinus, which lies roughly around the base of the posterior leaflet; (c) the bundle of His, situated close to posteromedial commissure; and (d) the non-coronary and left coronary aortic cusps, located adjacent to the base of the anterior leaflet (**Figure 3**). The aorto-mitral curtain, composed mainly of muscular fibers, while separating aortic and mitral structures, serves as inch point during systolic phase for counterbalancing the mitral tethering forces (9).

ANNULOPLASTY TECHNIQUES

The implementation of annuloplasty technique in the mitral valve repair has been initially developed in the surgical setting to restore the normal annular shape and dimensions by correcting posterior annular dilatation in symptomatic FMR patients. A standard surgical treatment comprises of annular ring reduction, aiming to improve leaflet apposition, relieve tension on the leaflets by optimizing the coaptation zone, preserve leaflet mobility, and prevent further annular dilatation.

There are various surgical annuloplasty devices on the market, including flexible or semirigid rings. Ring sizing is performed following Carpentier's principles, while the intra-operative measurement involves the intercommissural diameter and the area of the anterior leaflet.

Transcatheter annuloplasty has been developed in the field of transcatheter MV repair to fill the therapeutic gap for high-risk surgery patients with FMR and to prove its position as a solid percutaneous alternative to the edge-to-edge treatment or an adjuvant strategy among the FMR patients. In the recently published study, apart from the improvement of mitral parameters and symptoms, the investigators demonstrated that the use of Cardioband (Edwards Lifesciences) might result in lower rehospitalization and mortality when compared to MitraClip treatment (Abbott), especially when low-LVEF patients are concerned (10).

There are currently a number of devices under investigation for both indirect and direct percutaneous approach. Indirect techniques depend on the device introduction and placement within the MA through the parallel coronary sinus, whereas direct annuloplasty requires retrograde access to the left ventricle or trans-septal puncture. The latter techniques deliver the device within the close proximity of the MA (**Table 1**; **Figure 4**).

The method of direct transcatheter annuloplasty is a recognized therapy for inoperable MR patients, which offers a safer profile when compared to conventional surgery. Although it represents a technically complex procedural approach, it eliminates some of the anatomical restrictions of the indirect technique. These limitations comprise the variable distance between the coronary sinus and the annular plane, as well as the frequently close location of the circumflex artery exposed to iatrogenic injury. To date, there are two CE-approved direct annuloplasty devices, the Cardioband (Edwards Lifesciences) and the Mitralign (Mitralign Inc.).

PROCEDURAL PLANNING AND ECHOCARDIOGRAPHIC EVALUATION FOR PATIENT SELECTION

Patients referred to transcatheter mitral valve repair are those whose high surgical risk represents a main contraindication for open-heart valve treatment. The exception to this standard may be considered when a concomitant coronary artery disease requires adjuvant revascularization. When a patient is deemed inoperable, anatomical factors should carefully be considered for the selection of the appropriate intervention. Echocardiography, mostly TEE, is decisive for this aim.

Echocardiographic Evaluation of FMR

The FMR is typically characterized by the unaltered leaflet structure; however, one should expect other abnormalities

Abbreviations: MR, mitral regurgitation; FMR, functional mitral regurgitation; HF, heart failure; LV, left ventricle; MAC, mitral annular calcification; CT, computed tomography; TEE, transesophageal echocardiography; MA, mitral annulus; LV, left ventricle; LAD, left anterior descending (artery); LA, left atrium; AF, atrial fibrillation; PL, posterior leaflet; AL, anterior leaflet; CABG, coronary artery bypass grafting; ICE, intracardiac echocardiography.

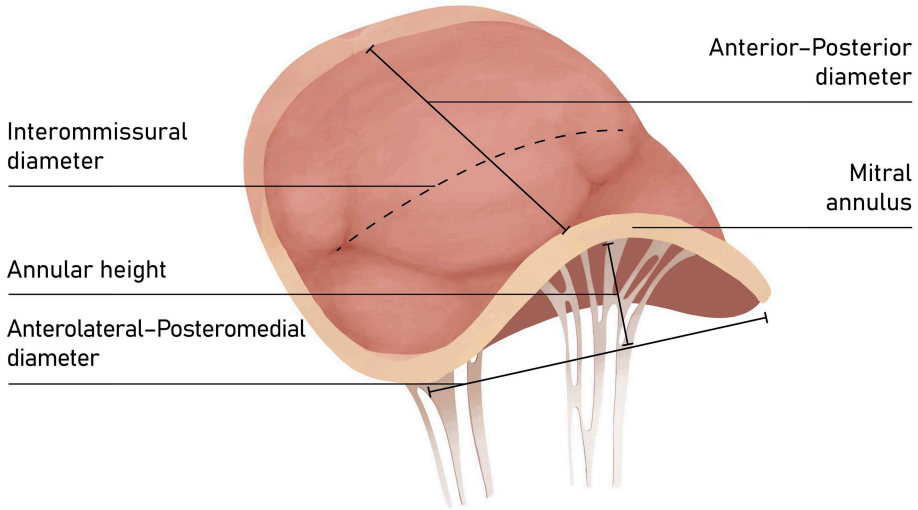

FIGURE 1 | The saddle-shape configuration of the mitral valve. The nonplanar shape is believed to significantly reduce the mechanical strains on the posterior leaflet during systole and optimize force distribution among mitral apparatus.

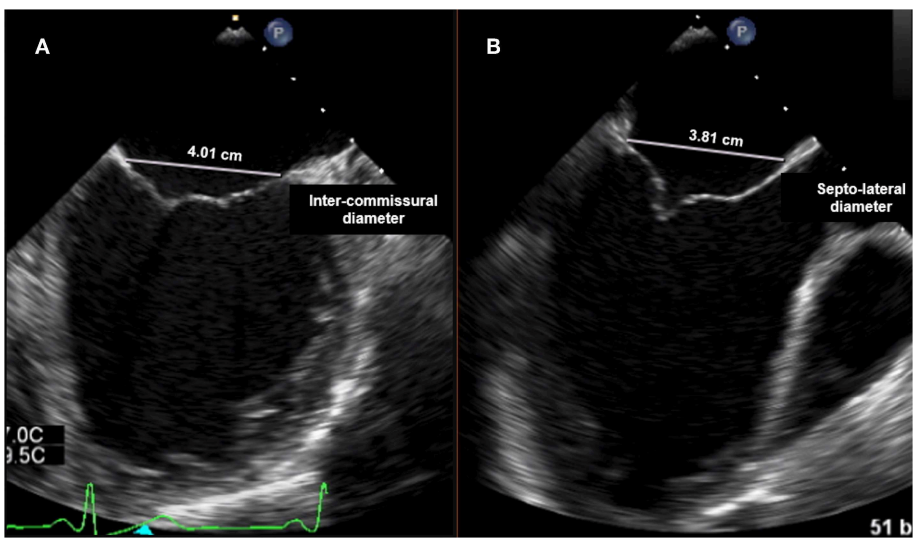

FIGURE 2 | Transesophageal echocardiography (TTE): **(A)** intercommissural view focused on MV for intercommissural diameter measurement; **(B)** mid-esophageal Long-axis view (ME LAX View) for septo-lateral (antero-posterior) annulus measurement.

(e.g., ruptured chords, flail leaflet) that would imply primary pathology. In addition, quantitative assessment of some mitral apparatus structures facilitates the understanding of the valve disease etiology and may influence future screening and procedural planning (**Figure 5**).

The presence of leaflet apical tethering resulting in the apically displacement of coaptation point is a decisive echocardiographic feature of FMR. Noteworthy, the leaflet tethering forces cause impaired leaflet coaptation within the annular plane, resulting in incomplete closure. Carpentier's classification of dysfunction is based on the opening and closing motions of the mitral leaflets in relation to the annular plane. The FMR can be defined according to Carpentier mechanisms as type I and type III (11). Type I FMR is less frequently causing severe MR and it is related to annular dilatation with normal leaflet motion. Isolated LA dilation, without LV enlargement or dysfunction, was previously demonstrated to be not sufficient for determining significant FMR (12). On the contrary, a recent study revealed that mitral leaflet area (MLA) adaptation, which occurs as a compensatory mechanism among patients presented with atrial fibrillation (AF) and isolated annular dilatation without LV dysfunction, becomes insufficient with greater annular dilatation (13, 14). The prevalence of type I FMR is growing due to aging of the population, increasing prevalence of concomitant long-standing

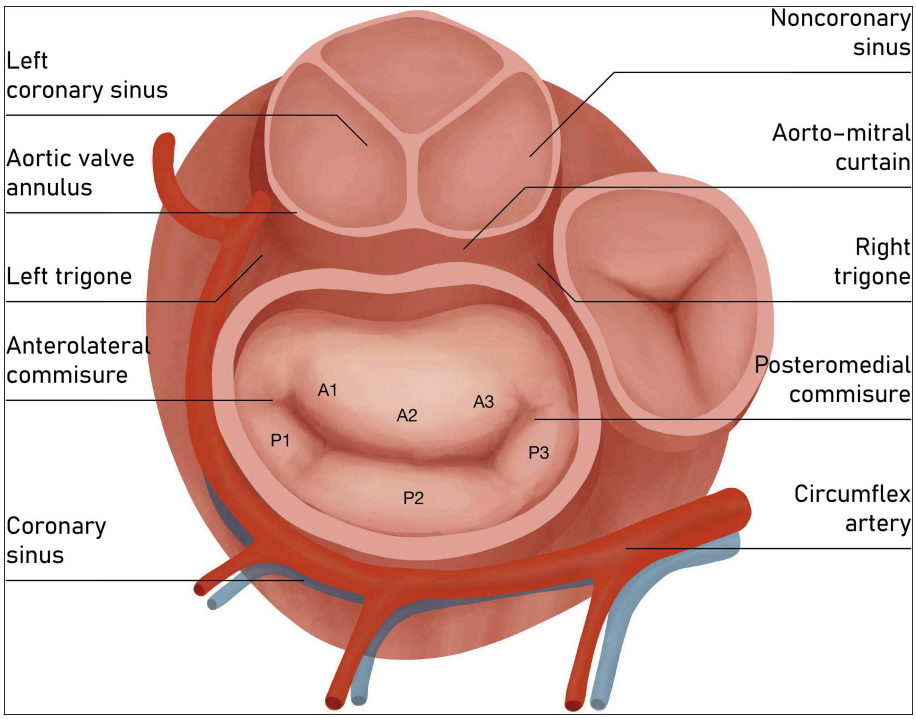

FIGURE 3 | Atrial view of mitral valve. Components of mitral valve apparatus and the adjacent structures. The posterior leaflet of the mitral valve composes ~3/5 of the annular circumference and comprises three individual scallops identified as P1 (anterior or medial scallop), P2 (middle scallop), and P3 (posterior or lateral scallop). The three corresponding segments of the anterior leaflet are A1 (anterior segment), A2 (middle segment), and A3 (posterior segment).

TABLE 1 | Currently available transcatheter direct annuloplasty systems (transapical approach devices have not been listed).

	Cardioband (Edwards Lifesciences)	**Mitralign (Mitralign Inc.)**	**Millipede (Boston Scientific Corp.)**
Access	Transseptal	Retrograde	Transseptal
Position	Supra-annular	Cross-annular	Supra-annular
Repositionable	Yes	Yes	Yes
Clinical status	CE Mark	CE Mark	Investigational use

persistent AF, and impaired LV diastolic function. In non-ischemic MR, usually the tethering is symmetric and the jet is central (**Figure 5**).

In the incidence of ischemic FMR (type IIIb), the displacement of the papillary muscles and distortion of LV directly alter the geometry and function of the mitral valve apparatus. Although both papillary muscles are frequently affected, it is the dysfunction of posterior papillary muscle that prevails and results in the tethering of the posteromedial leaflet segment (P3) (**Figure 6**). Hence, FMR jet is usually eccentric and directed posteriorly along the P3 area (**Figure 7**) (15). However, in the case of unpopular LAD infarction, the large central MR jets mark the preceding broad ischemia of the papillary muscles and other affected LV segments (16). With the increase of lateral and apical forces, the leaflet tethering predominates over annulus dilatation. In that case, the annuloplasty as a stand-alone procedure is typically not a sufficient repair therapy. Numerous surgical methods have been introduced to address the left ventricle dilatation (e.g., papillary muscle approximation, ventricular containment/ventriculoplasty). Nonetheless, having in mind further LV remodeling in the course of the secondary MR, the "downsizing" of the mitral annuloplasty (i.e., restrictive mitral ring implantation) may be recommended (14, 16, 17).

Patient Selection and Success Predictors of Annuloplasty Techniques

Echocardiographic assessment should consistently clarify if the mechanism of MR is functional and at the same time evaluate the LV dimension and function to distinguish type I from type III FMR. Once the MR mechanism is determined, further TEE assessment is crucial for selecting the suitable patient for the right procedure (see section Anatomical Factors: MV Leaflet Tethering).

Presuming that MR is successfully treated with MitraClip, given the large amount of evidence, transcatheter edge-to-edge treatment may be regarded as a first-line procedure. Nonetheless, in the case of annular dilatation, one should consider annuloplasty techniques. In fact, this procedure "leaves the door opened" to other supplementary treatment (18, 19).

Evaluation of remodeling of MV apparatus and LV can facilitate the prediction of the MR recurrence after annuloplasty. From an anatomical perspective, the rationale of both surgical

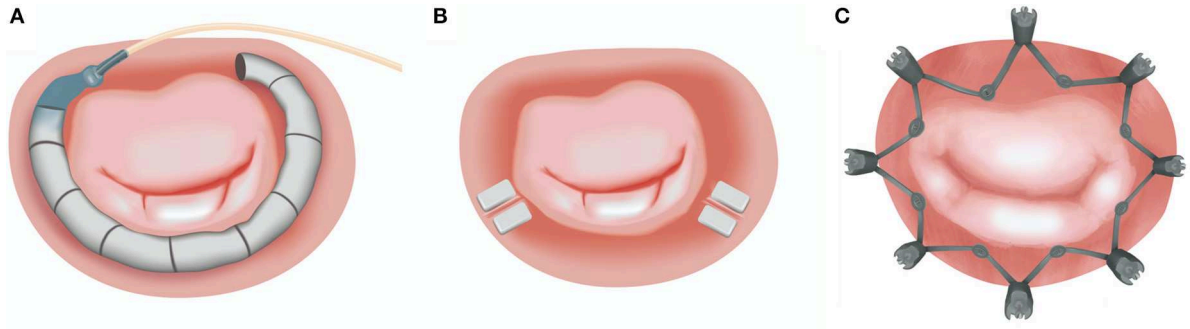

FIGURE 4 | Currently available transcatheter direct annuloplasty systems: **(A)** Cardioband (Edwards Lifesciences); **(B)** Mitralign (Mitralign Inc.); **(C)** Millipede (Boston Scientific Corp.). Image Courtesy of Millipede, Inc. www.millipedemedical.com All rights reserved.

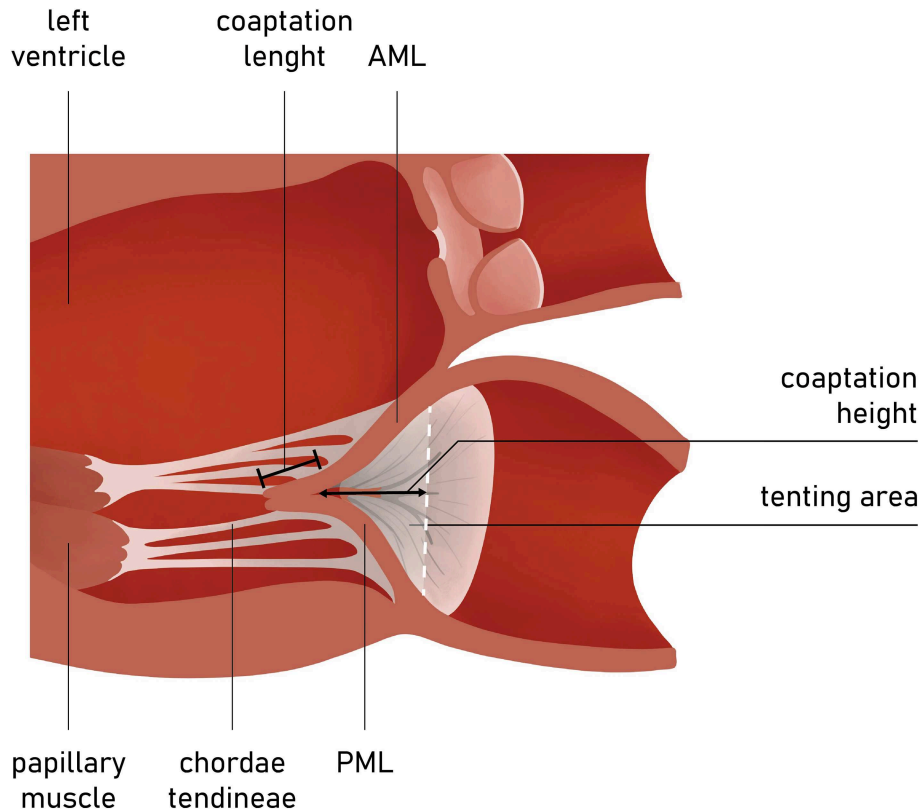

FIGURE 5 | Long-axis view of the LV and MV apparatus. Coaptation length, height, and tenting area are among key measurements in the preoperative planning and screening.

and transcatheter annuloplasty depends on shifting the posterior annulus anteriorly, reducing the septolateral distance and increasing the coaptation area. However, this mechanism does not settle anteriorly the coaptation point, since the posterior leaflet struggles being tethered posteriorly and its anterior excursion is noticeably limited. This phenomenon of "freezing of posterior leaflet" is always present after annuloplasty and does not affect the anterior leaflet (AL) motion, so that valve closure becomes essentially a "single-leaflet process" and the frozen posterior leaflet (PL) serves only as a support for the closure (16).

Anatomical Factors: MV Leaflet Tethering

Some MV geometry parameters have been found to be independent predictors of the recurrence of MR after MV ring annuloplasty. Previous studies have demonstrated that poor outcomes of the surgical annuloplasty may be associated with greater preoperative leaflet tethering. Calafiore et al. have determined that a coaptation distance of more than 1.1 cm might be associated with a high risk of MR recurrence after surgery (17). Likewise, a similar study of patients who underwent ring annuloplasty revealed that one should consider a posterior

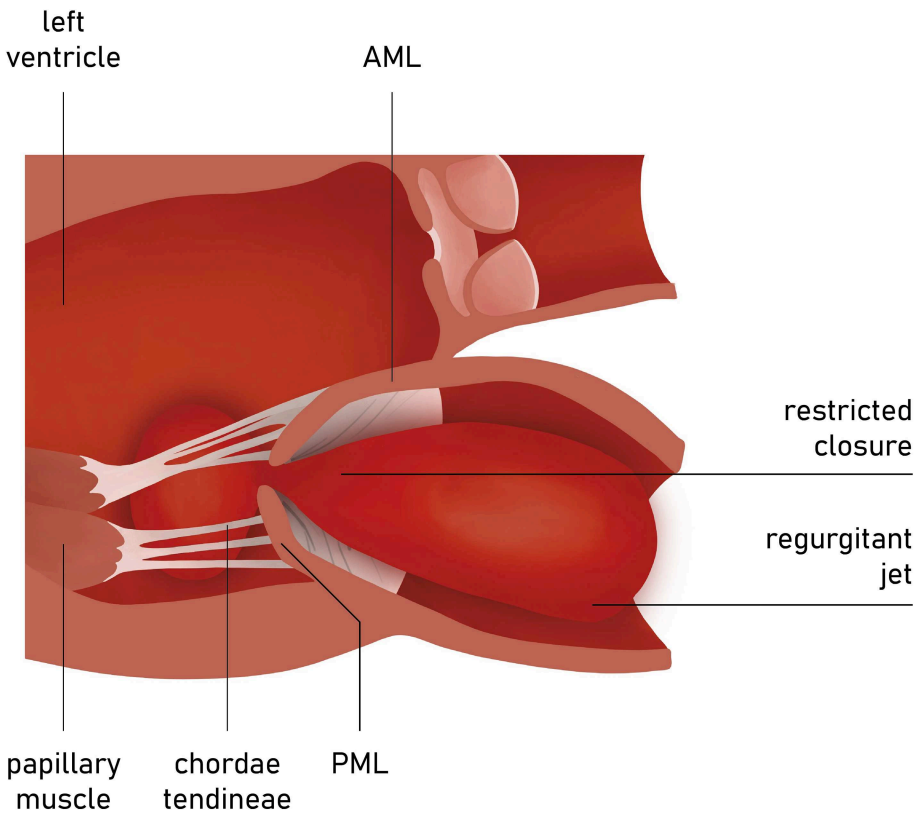

FIGURE 6 | Carpentier type I mitral regurgitation (depending from annular dilatation). Normal leaflet motion. Regurgitation jet directed centrally.

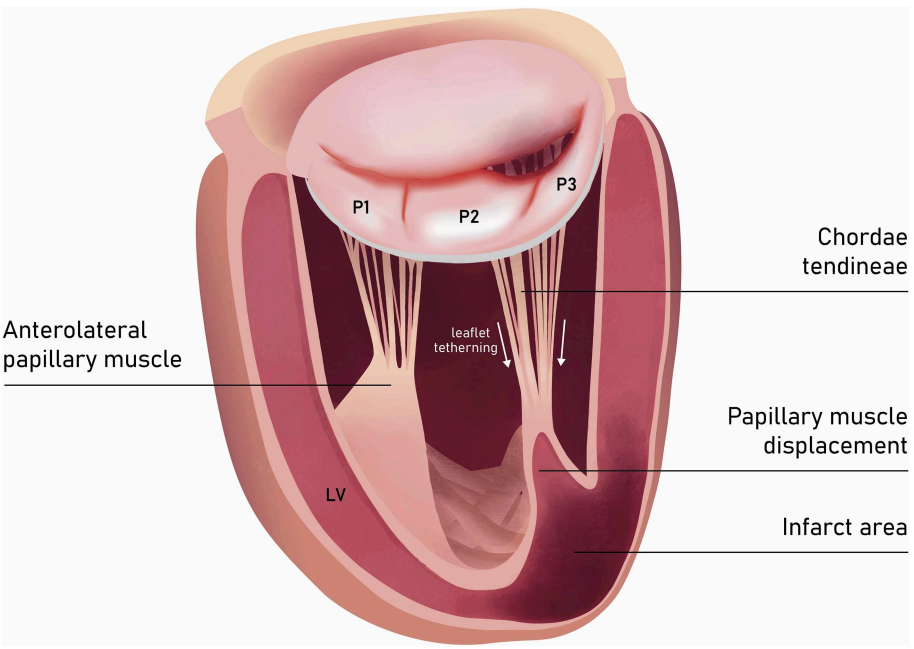

FIGURE 7 | Left ventricle and mitral valve—side view (LVOT was not depicted). The restricted leaflet motion and tethering in the course of posterior papillary muscle ischemia predominantly affects the posteromedial leaflet segment (P3).

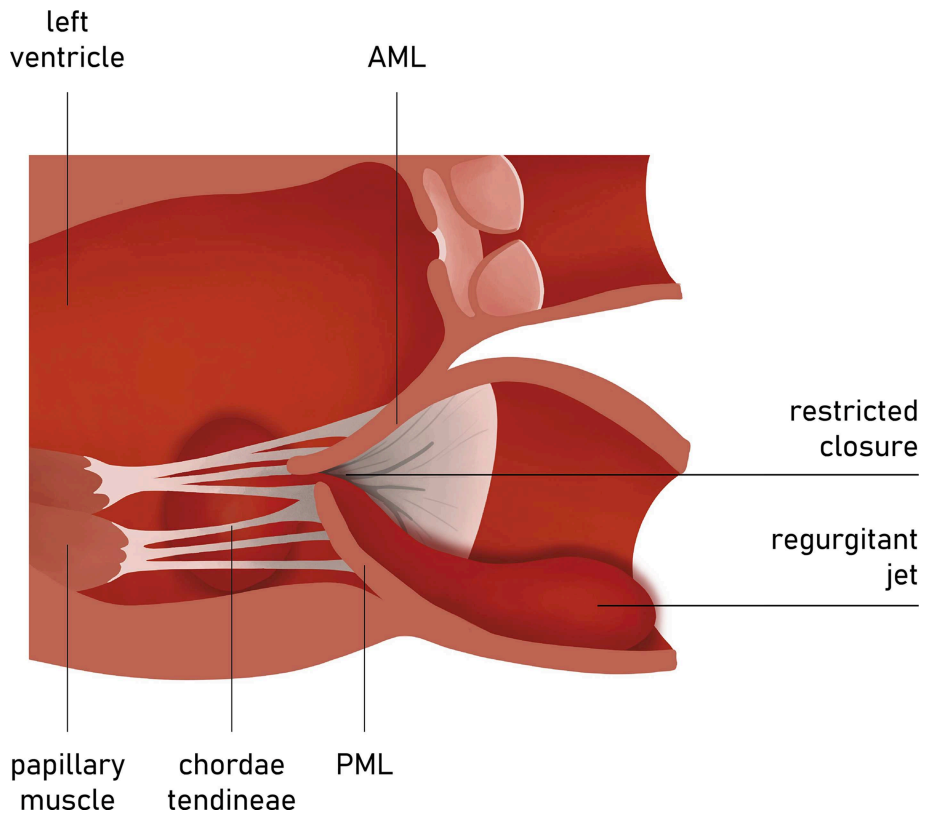

FIGURE 8 | Carpentier type III mitral regurgitation. Restricted leaflet motion. Regurgitation jet directed eccentrically.

leaflet angle of more than 45°, a tenting area above 2.5 cm^2, and the coaptation distance of more than 1 cm to predict the persistence of more than moderate MR after surgical annuloplasty (19). Considering the small amount of data of new-generation annuloplasty techniques, these parameters might also serve as a reference for transcatether MV repair (19–21).

A tethering direction has been regarded as a determinant for the symmetry of the leaflet restriction. The properly functioning chordae system comprises the marginal part that fixes the free edges of both mitral leaflets and the stiffened basal part that constitute the base of the ventricular side of AL. Anterior leaflet tenting angles can be identified as basal and apical (**Figure 8**). Since the insertion points of chordae vary, the direction of tethering forces creates different geometrical shapes of tenting area and leaflets. When the posterior tethering predominates, the tethering of the basal chordae on the medial part of AL is more pronounced than the tethering of distal-primary chordae on the anterior leaflet tips. As a result, the AL structure tends to bend. This effect might be restored by reducing the posterior dilatation and the tethering on basal chordae. However, in the incidence of the apical tethering of both leaflets, the motion of distal AL is usually restricted, creating more challenging conditions for the successful annuloplasty (22). Hence, jet eccentricity, direction, and distal anterior leaflet tenting angle are currently regarded as the determinants for predicting the success of annuloplasty techniques, more than a basal anterior leaflet tenting angle and posterior tenting angle (23, 24). Annular size and calcifications as well as the proximity of the circumflex artery are also acknowledged factors of the feasible and successful direct annuloplasty.

Functional Factors: Left Ventricle Remodeling

Many studies, including more than 700 patients treated with MV annuloplasty, sought to identify the factors that correlate with mitral annuloplasty outcomes. In one analysis, the investigators revealed that the recurrence of MR within the first 6 months was associated with higher grade of preoperative MR, smaller body size, early date of operation, jet direction other than posterior (essentially central or complex), and the Peri-Guard annuloplasty technique (25). Subsequent MR recurrence (>6 months) was related to severe preoperative left ventricular dysfunction (26). More recently, a re-analysis of 214 patients with ischemic FMR by the Cardiothoracic Surgical Trials Network (CTSN) investigators, has demonstrated that the 1-year recurrence of MR is linked to LV end-systolic diameter/ring size mismatch, after adjustment for age, sex, and baseline LVEF. A basal aneurism or dyskinesis of LV was associated with significant recurrent MR, rebating the role of higher LV–MV ring mismatch that is obviously more pronounced in case of basal aneurysms (26, 27). In a small group of patients undergoing MV ring annuloplasty, it was demonstrated that the LV sphericity index, calculated at end-systole as the volume of LV divided by the volume of a sphere

TABLE 2 | Predictors of failure of annuloplasty evaluated in surgical setting.

Predictors of recurrent MR after surgical annuloplasty
Short-term results
Distal anterior leaflet angle tethering
Leaflet tethering: tenting depth (height) and tenting area
Higher grade of preoperative MR
Smaller body size
Early date of operation
Jet direction other than posterior (essentially central or complex)
Peri-Guard annuloplasty technique
Mid- and long-term results
Severe LV dilatation and dysfunction
LV sphericity
Ratio between LVESD/ring size (mismatch)
Basal aneurysm/dyskinesis
Clinical factors/past history (age, body mass index, sex, race, NYHA, prior CABG, prior percutaneous coronary intervention, and history of ventricular arrhythmia)

with a diameter equal to the LV longest axis (measured in apical view), was the best predictor of long-term recurrent MR. Indeed, this parameter conveys the degree of tethering, as the more spherical is the LV, the more the displacement of the papillary muscle (25). Keeping in mind that advanced LV remodeling is associated with worse outcomes, in the subgroup of patients with enlarged ventricle and great tenting height (particularly >11 mm), not only the annuloplasty, but a subvalvular repair might be necessary (28).

It has to be noted that all these factors (anatomical and functional) derive from surgical setting and further studies are necessary to prove them as predictors of the recurrence of MR after transcatheter annuloplasty. Despite the lack of evidence, these criteria can be useful in preoperative evaluation of patients candidate to transcatheter annuloplasty for predicting the risk of procedural failure. Noteworthy, in the intraprocedural setting of transcatheter intervention, these factors can be re-evaluated right after the restrictive annuloplasty in order to plan further staged or even combined interventions (**Table 2**) (17, 18).

CORONARY ANGIOGRAPHY AND COMPUTED TOMOGRAPHY (CT)

The presence and significance of possible coexisting coronary artery disease need to be documented; therefore, coronary angiography is routinely performed. Over the years, together with a rapid development of percutaneous interventions, computed tomography imaging has become a decisive tool for the preprocedural planning and implant selection. CT reconstructions allow a comprehensive assessment of mitral valve anatomy and can be a valuable tool to predict procedural challenges such as the proximity of the adjacent structures, in particular the circumflex artery and the risk of its injury (29, 30). Along with the MV annular size and aortic and mitral valve correlations, the optimal transseptal puncture site is selected. Secondly, the posterior annulus is divided into multiple regions to identify the right position and indicate the anchor angle. Finally, optimal fluoroscopic planes for implantation should be estimated. Keep in mind that mitral annular calcification might be considered as a contraindication for mitral annuloplasty, as severe MAC hinders optimal anchoring and contracting of the implant and may also deteriorate echocardiographic image quality (**Figure 9**).

CARDIOBAND MITRAL SYSTEM (EDWARDS LIFESCIENCES)

The early experience with the Cardioband proved that this direct annuloplasty device is feasible, safe, and effective. The implantation is performed under general anesthesia with fluoroscopy and 3D-echo guidance in a stepwise fashion. While proceeding with the procedure, every move is reversible, resulting in a legitimate safety level and control.

The Cardioband system uses a transseptal steerable sheath (TSS) that is delivered over a super-stiff guide wire via the femoral vein into the left atrium by a standard transseptal puncture. By that time, make sure to obtain an activated clotting time between 250 and 300 s. The steerable sheath facilitates the optimal positioning of the implant catheter possibly close to the leaflet hinge, near the anterior commissure. Verification of the first anchoring location is crucial and requires echo supervision to prevent the damage of surrounding structures. To rule out the risk of circumflex artery injury, coronary angiography is performed. The use of a standard 0.014″ coronary wire may serve as a radiographic marker and a potential railway for bailout PCI-LCx. Regardless of the assessment, the operator needs to be prepared for a possible bail-out scenario (**Figure 10**) (31). The depicted vessel might also serve as a useful reference to guide the procedure. After the first implant is delivered at the anterolateral trigone and its position is verified, a set of anchors is advanced through the polyester sleeve into the annular part in the posterior and medial correspondence to the first implant. Every anchor is deployed until the radiopaque marker on the Implant Catheter Channel reaches the next marker on the implant. Before every release, the operator needs to verify proper anchoring of the implant with "push-and-pull test" under echo and fluoroscopic guidance. Please note that the implantation of the anchors with an angle of 45° can improve the fixation permanence. The number of anchors depends on the size of the device implanted and are usually delivered every 8 mm until the Implant Catheter tip reaches the final anchoring position on the posterior commissure. Usually, during the anchor implantation into the myocardial tissue, extra-systolic beats on the ECG can be observed. When the final anchor is deployed, the implant is detached from the delivery system and removed. Once the entire device is implanted, the contraction wire with "size adjustment tool" is advanced over the implant guide wire, until the distal tip reaches the "adjustment spool" of the implant. The implant is then contracted by clockwise turn of the "adjustment roller" until the appropriate size is reached. Typically, a left anterior oblique

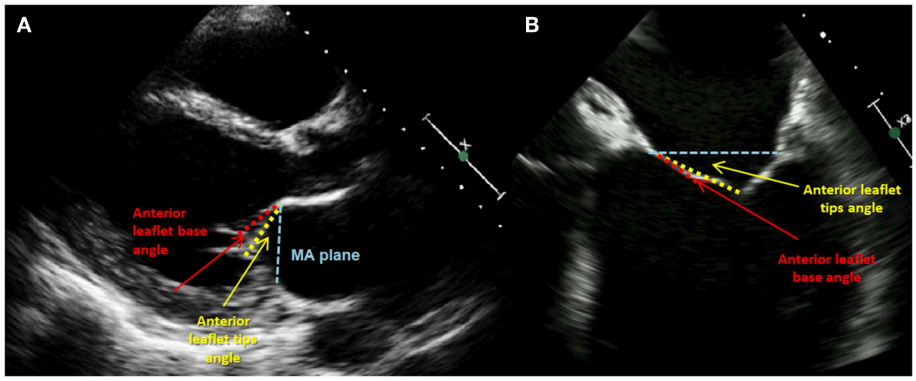

FIGURE 9 | Phenotypes of tethering. **(A)** Transthoracic echocardiography (TTE), parasternal LAX view: anterior leaflet (AL) tethering with AL bend; **(B)** transesophageal echocardiography (TTE), midesophageal 4-CH view focused on MV: less pronounced bend and tip angle of the AL.

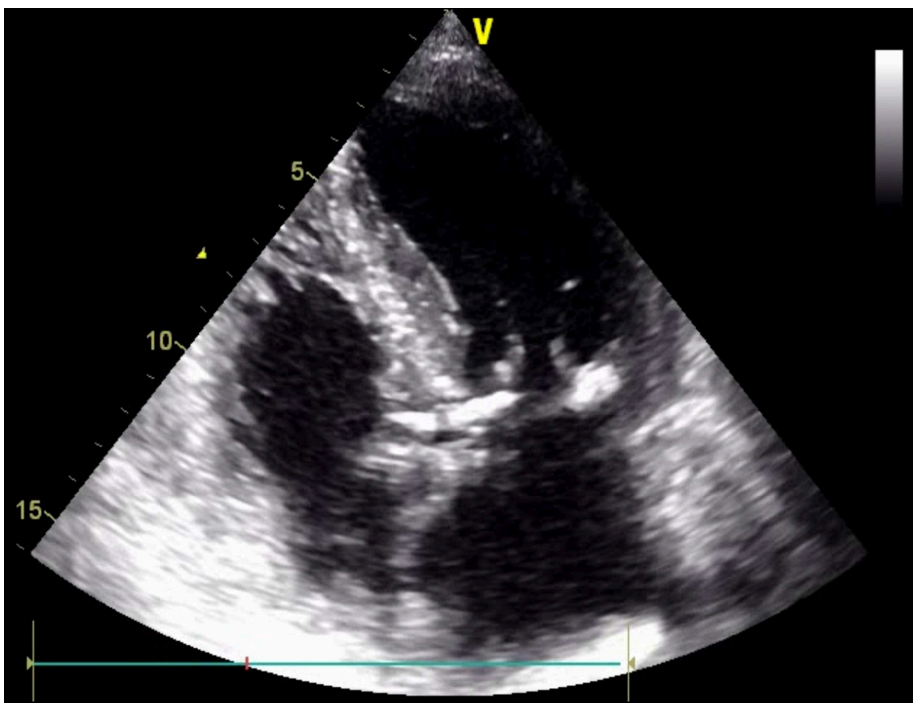

FIGURE 10 | Transthoracic echocardiography (TTE); apical 4-CH view. Mitral annular calcification (MAC).

(LAO) projection is used to guide this step. Finally, the obtained reduction of MR is evaluated by TEE under beating-heart setting (**Figures 11**, **12**).

The key advantages of the system are adjustable implantation with the real-time confirmation of the result due to echo-driven live imaging and the instantaneous improvement of the patient's hemodynamics. The device preserves the patient's native anatomy, keeping future treatment options open in case of recurrent MR. The recent studies proved the efficacy and safety of the Cardioband implantation, which resulted in a significant MR reduction in majority of patients and was associated with significant improvement in functional status and quality of life (32). The ongoing ACTIVE randomized trial is expected to support these early promising results (NCT03016975).

THE MITRALIGN (MITRALIGN INC.)

The Mitralign uses a retrograde approach to deliver a 14-Fr guiding catheter through the aortic valve, onto the posterior side of the left ventricle, beneath the mitral leaflet. Two pairs of wires are advanced through the MA tissue and deliver the pledges on both sides of the commissure. The first pledged catheter extrudes half the pledget on the atrial side and the other on the ventricular

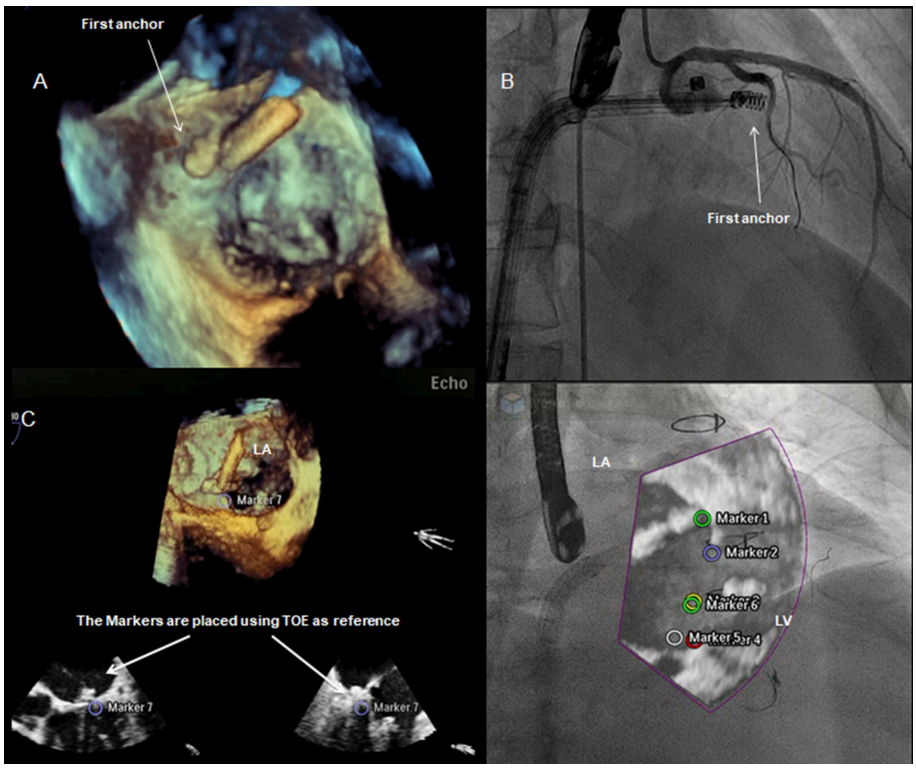

FIGURE 11 | Integrated intra-procedural guidance for Cardioband: **(A,C)** real-time 3D transesophageal echocardiography facilitates the navigation and delivery of the first anchor; **(B)** fluoroscopy: the use of coronary wire may serve as a radiographic marker and a potential railway for bailout strategies. Fusion imaging allows to display an overlap image of the "echo-structures" in the fluoro-images. This could be a valuable tool in the presence of difficult anatomies and in the first phase of the operator's learning curve.

side. The delivery of the second pledged catheter follows the same steps. Both anchors are connected by a drawstring, and by tightening up the sutures, the reduction of MA is achieved. When the same steps are followed on the opposite side of the valve, the procedure is complete. With the Mitralign System, the perimeter of the annulus can be reduced by as high as 20%. The device is assigned to FMR patients, addressing MV annular dilatation. The key advantage of this technique is that the transseptal puncture is not needed during the procedure. However, in patients with depressed LV function, the retrograde access may be less tolerated. In the "Mitralign Percutaneous Annuloplasty First-in-Man Study," the device proved the favorable safety profile while reducing the MR grade and symptoms in 50% of patients during 6-month observation (33).

MILLIPEDE TRANSCATHETER ANNULOPLASTY RING (BOSTON SCIENTIFIC CORP.)

The direct transcatheter-based annuloplasty approach from Millipede features a complete semi-rigid ring designed to reproduce the surgical MV repair. The delivery system includes the guide catheter, the delivery catheter, and the ICE catheter. Introduced by transfemoral, the venous approach is delivered through the transeptal puncture above the mitral valve annulus. The delivery catheter settles the device supra-annularly just before the anchoring. Finally, the ring is clinched, resulting in the annular size reduction (anterior–posterior diameter). The mechanism is designed to provide reposition and retrieve options during the procedure, while preserving the possibility for further sub-valvular treatment after complete implantation. The procedure is guided by the compound, but standard imaging: fluoroscopy to assess the atrium, TEE to land the device, and ICE to locate the anchors. The introduced steering method facilitated by the ICE imaging might be particularly convenient for experienced MitraClip implanters. To date, the device proved encouraging safety profile and efficacy in reducing MR. The technology is still under development and not available for commercial use (34).

CONCLUSIONS

Patients with severe MR regarded too high risk for surgery can benefit from novel percutaneous approaches. Current imaging modalities have contributed to understanding the etiology and anatomy of MR, and are an integral part of preprocedural planning. Considering that TEE and CT offer a comprehensive 3D assessment, they are regarded as the gold standard for MR

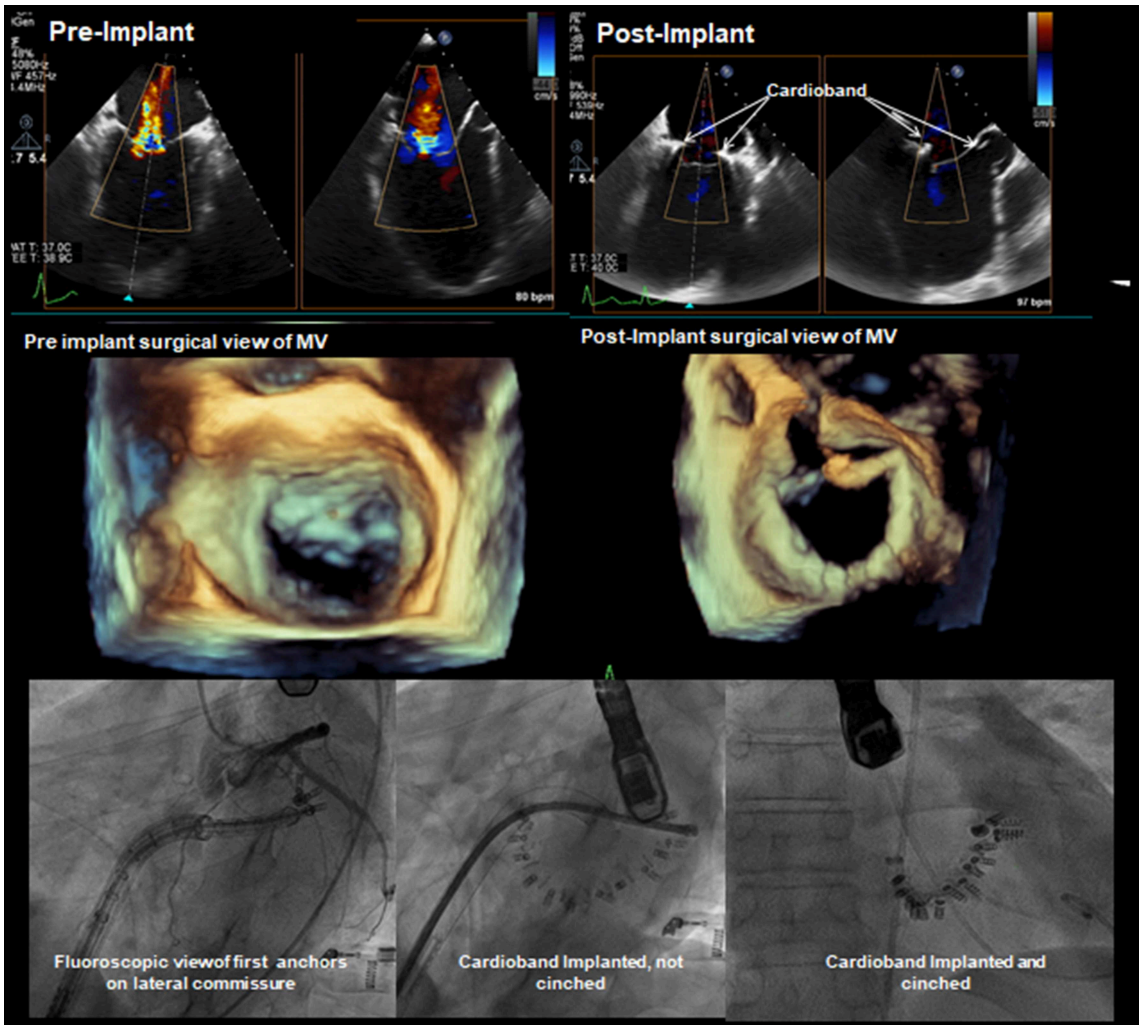

FIGURE 12 | Pre- and post-implantation echo and fluoroscopy images. TEE 2-CH and LAX projections demonstrating visibly reduced regurgitation jet. Fluoro images showing the process of deployment and clinching of the annuloplasty ring concluded with a successful implantation.

evaluation and the optimal patient selection. The enhanced live visualization of the mitral apparatus due to the fusion of 3D-echo and fluoroscopy can provide more intuitive imaging and facilitate the intraprocedural guidance at any stages of the annuloplasty procedure (33).

The direct percutaneous mitral annuloplasty addresses the underlying mechanisms of FMR with a less invasive, catheter-delivered approach. In previously conducted studies, based on surgical experience, the investigators demonstrated that the combination of leaflet repair with surgical annuloplasty has a potential for a lower rate of MR recurrence (35). Although the percutaneous annuloplasty devices are primarily intended for the stand-alone treatment of FMR, the simultaneous usage of two therapies may become an alternative strategy for some subgroups (36). Therefore, Latib et al. proved the feasibility of percutaneous direct annuloplasty as a treatment option for patients with FMR previously subjected to MitraClip and presented with persistent annular dilation and recurrent MR. As in surgical setting, the direct transcatheter annuloplasty may serve as a part of the combination strategy with a percutaneous edge-to-edge repair for individuals with a functional impairment of mitral valve and asymmetric tethering to obtain lower rates of MR recurrence. Yet, this has to be proven in further clinical trials. Moreover, some patients screened for MitraClip are considered unsuitable, indicating that there is a clinical need for an adjunctive transcatheter mitral repair strategy (37–39). This group primarily includes individuals with calcified or rheumatic deformed leaflets and substantial annular dilatation. Although there has not been any cutoff for the annular dimension established, one may consider a range between 40 and 45 mm too much for the edge-to-edge therapy as a first-line procedure. However, in some cases, despite the extensively dilated annulus, the length of the leaflets may still allow sufficient coaptation. One should consider isolated annuloplasty procedure for an early treatment of the FMR, while the ideal patient for that indication might be regarded as the one with limited tethering of the posterior leaflet or with the isolated

atrial enlargement with a concomitant annular dilatation (in the absence with LV remodeling).

The recently published propensity matched analysis of registry data demonstrated that both edge-to-edge treatment and direct annuloplasty effectively reduce MR and heart failure symptoms. However, FMR patients treated with Cardioband proclaimed more notable improvement regarding NYHA scale, rehospitalization, and mortality, with predominant benefit in the EF < 30% subgroup (40).

The here-described devices proved to be safe and effective, providing significant MR reduction in the study group and significant improvement of symptoms (30, 31). Finally, the simultaneous training of interventional cardiologists, cardiosurgeons, and echocardiographers, and reproducibility of the procedure are the key points to achieve more optimal results with less procedural times. Having in mind all mitral therapeutic options, current cardiovascular medicine offers a therapy based on the mechanism of MR with new approaches likely to set a new standard of treatment in the forthcoming future.

AUTHOR CONTRIBUTIONS

TG: literature selection, personal experience, and main contribution in paper writing. MG: literature selection, personal experience, and second-main contribution in paper writing. MT: paper structure conception, paper writing guidance, and practical experience. MZ and FM: medical consultation and practical experience.

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frontiers in Cardiovascular Medicine

REVIEW
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Mitral Regurgitation: Anatomy, Physiology, and Pathophysiology—Lessons Learned From Surgery and Cardiac Imaging

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The normal mitral valve is a dynamic structure that permits blood to flow from the left atrial (LA) to left ventricle (LV) during diastole and sealing of the LA from the LV during systole. The main components of the mitral apparatus are the mitral annulus (MA), the mitral leaflets, the chordae tendineae, and the papillary muscles (PM) (**Figure 1**). Normal valve function is dependent on the integrity and normal interplay of these components. Abnormal function of any one of the components, or their interplay can result in mitral regurgitation (MR). Understanding the anatomy and physiology of all the component of the mitral valve is important for the diagnosis, and for optimal planning of repair procedures. In this review we will focus first on normal anatomy and physiology of the different parts of the mitral valve (MA, leaflets, chordae tendineae, and PM). In the second part we will focus on the pathologic anatomic and physiologic derangements associated with different types of MR.

Keywords: mitral regurgitation, mitral annulus, papillary muscles, left ventricle, left atrium

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MITRAL VALVE APPARATUS ANATOMY AND PHYSIOLOGY

Mitral Annulus

The mitral annulus (MA) is defined by the tissue intersection between the LA, LV, and the mitral leaflets. It is dynamic throughout the cardiac cycle, is made out of parallel collagen fibers and is well-defined histologically. It is non-planar and shaped like a saddle (**Figure 1**, **Supplementary Movie 1**) (1, 2). The anterior portion of the MA is continuous with the aortic annulus and constitutes the most atrial part of the saddle shape (2). The posterior part of the MA includes the lowest points of the saddle close to the lateral and medial commissures. Compared with the anterior portion, the posterior MA is not anchored strongly to the neighboring tissue, allowing more free movement during myocardial contraction and relaxation.

The angle between the MA to the aortic annulus changes during the cardiac cycle through the mitral aortic fibrous continuity (3). Recent studies, using 3-D echocardiography (1, 4, 5) have assessed the normal mitral annulus changes over the cardiac cycle. They have showed that variation of annular size throughout diastole is minimal. However, in early-systole, during the iso-volumic contraction period, antero-posterior contraction occurs, resulting in folding across the fixed inter-commissural diameter. This contraction leads to very early-systolic annular area contraction, accentuation of saddle shape, and approximation of anterior and posterior leaflets. In other words, when early-systolic ventricular pressure is still relatively low, leaflet approximation by annular contraction and saddle shape accentuation results occurs even before LV pressure rises, locking the

leaflets together. This mechanism may be important in preventing early systolic mitral regurgitation (**Supplementary Movie 1**). The mechanism for this early saddle-shape accentuation is disputed. Some have postulated it is related to tethering of the anterior annulus to the aortic root combined with apical translation of the "loose" posterior annulus resulting in folding across the inter-commissural axis.

The MA is innervated and supplies blood vessels to the leaflets (6, 7).

Several recent investigations using advanced imaging modalities reported an average mitral annular area of ∼10 cm^2 in healthy subjects (8–10), much larger than the widely believed "normal" mitral annular orifice area of 4–6 cm^2.

Mitral Valve Leaflets

The mitral valve leaflets fully open and close up to 3,000,000,000 times throughout a lifetime (11). Despite this high burden, significant mitral valve disease is uncommon in patients younger than 65 years. The mitral valve has anterior and posterior leaflets and variable commissural scallops to occlude medial and lateral gaps (**Figure 2**). Leaflet tissue is attached to the MA, and the normal tissue length is between 0.5 and 1.0 cm (12). Redundant leaflet tissue is very important for tight leaflet co-aptation and sealing. The normal ratio of mitral annulus to mitral leaflet area is 1.5–2.0, and is vital to prevent significant MR in normal, and even dilated left ventricles (12). The normal atrial surface of the leaflets is smooth. A hydrophilic protein-rich part, called the rough zone, starts ∼1 cm from the distal leaflet tips and helps to ensure a perfect seal between the leaflets, termed the co-aptation zone. The ventricular surface of the anterior leaflet is made out of collagen fibers originating from the chordal insertion continuing up to the annulus. There are two types of chordae, the primary and secondary chords. The primary chords insert at the tips of the leaflets, but the secondary chords attach to the leaflets close to the rough zone (13). The anterior mitral leaflet is shaped like a sail, and is anchored to the fibrous portion of the MA. It is continuous with the fibrous tissue of the non-coronary cusp of the aortic valve (**Figure 2**). It is tightly anchored to the left and right fibrous trigones by collagen fibers (14). It is larger, longer, and thicker than the posterior leaflet (see **Figure 2**). The anterior

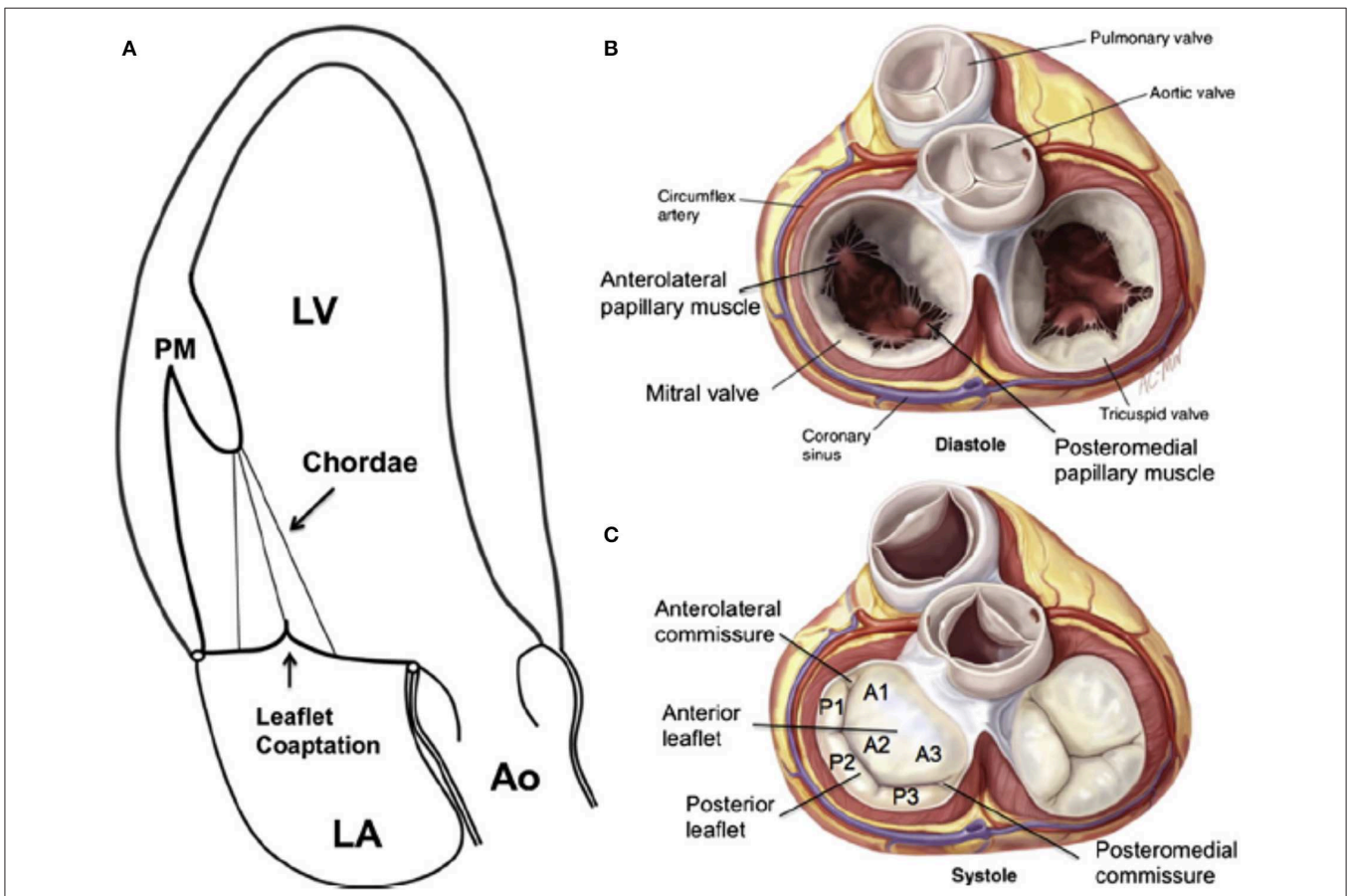

FIGURE 1 | (A) Apical long-axis view of the normal heart in systole. There is no tethering, both leaflets are normal, concave toward the LV, and co-aption is in the annular level. **(B)** The open mitral valve in diastole from the atrial view. **(C)** Surgical view of the closed mitral valve in systole showing the anterior "sail-like" leaflets with no indentations vs. the posterior segmented leaflet. A, anterior leaflet; Ao, aorta; LA, left atrium; LV, left ventricle; P, posterior leaflet; PM, papillary muscle. From Carpentier A. Carpentier's reconstructive valve surgery. St. Louis: Saunders/Elsevier; 2010; with permission.

leaflet is divided into lateral (A1), central (A2), and medial scallops (A3). However, for the anterior leaflet, this nomenclature does not represent real anatomically distinct structures, and the sub-division is done only to simplify medical communication (**Figure 2**).

The posterior leaflet is crescentic in shape and has a much longer circumferential connection (≈5 cm) to the MA compared with the anterior leaflet (≈3 cm). However, the posterior leaflets has a shorter radial length compared to the anterior leaflet (**Figure 2**). The posterior leaflet is also divided into lateral (P1), central (P2), and medial scallops (P3) just like the anterior leaflet. However, contrary to anterior leaflet it does have true slits within its tissue demarcating these scallops (see **Figure 2**) (15).

Commissural leaflets are composed of additional leaflet tissue found at the anterolateral (A1-P1) and posteromedial (A3-P3) commissures (see **Figure 2**) (12).

Histologically, the mitral leaflet tissue has three layers, including the fibrosa (on the ventricular surface), spongiosa (the mid layer), and atrialis. Endothelial cells cover the blood-interfacing surfaces on both atrial and ventricular surfaces. Each tissue layer has unique matrix characteristics. The fibrosa, that has to withstand the higher LV pressures, is composed of dense collagen, improving mechanical stability. The spongiosa has less organized collagen, but is rich in hydrophilic proteins at the tips ensuring a tight seal. The atrialis contains a rich network of collagen and elastin that may play a role in leaflet remodeling and adaptation (16). In both leaflets, cardiac muscle cells are present close to the annulus. This muscle tissue is excitable from the atrial side, apart and before LV excitation, and histologically resemble atrial myocardial calls (17). These muscle cells may contract even before the beginning of LV contraction and may play a role in the early closure of mitral leaflets observed before ventricular contraction. This early "leaflet" contraction may be important for avoiding early systolic regurgitation during the iso-volumic contraction period. Interstitial cells in leaflets are usually inactive, and their turnover is slow. Nevertheless, physiologic- or pathologic- induced leaflet stress can induce interstitial cell activation and proliferation (16). This proliferation suggests a potent adaptation mechanism, inducing leaflet augmentation during pathologic conditions associated with annular dilatation. Although both leaflets have three layers, their microstructure differs significantly. The anterior leaflet has to withstand a higher load and is composed mostly out of the fibrosa layer. On the other hand, the posterior leaflet is thinner and more flexible (18).

The anterior leaflet anterior also has an especially dense innervation compared with the posterior leaflet (19).

Chordae Tendineae

The chordae tendineae are fibrous cords originating from the papillary muscle (PM) tips that insert in a hand-held fan pattern into the ventricular aspects of the anterior, posterior, and commissural leaflets (see **Figure 2**) (20). Rarely, chordae emanate from the basal posterior segments of the left ventricle and attach directly into the posterior leaflet. There are two main types of chordae that can be differentiated based on leaflet insertion. The primary chords attach to the leaflet-free edges. The secondary chords attach to the anterior leaflet rough zone and throughout

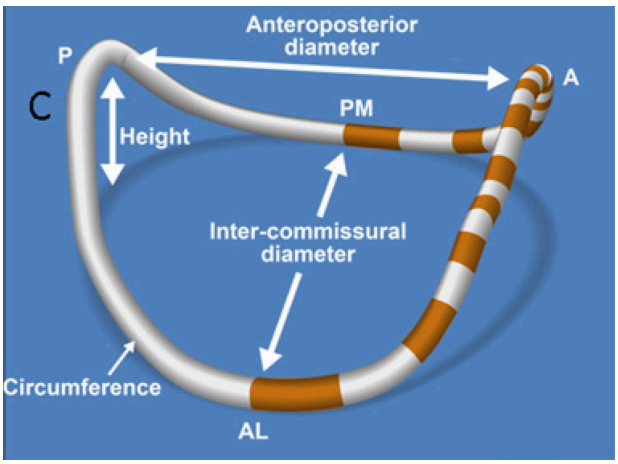

FIGURE 2 | Schematic representation of a 3D reconstructed mitral. annulus. AL, antero-lateral; PM, postero-medial; ML, medial-lateral (intercommisural) diameter; AP, antero-posterior diameter.

the posterior leaflet body (21). The Chords are made of tight collagen and elastin network that distribute chordal forces over the leaflet surface (20, 21). Primary chordae are thinner and have limited extensibility that prevents leaflet edge inversion and flail (22). On the other hand, secondary chordae are thicker, and have more elastin, making them more extensible. Chordal anatomy and branching patterns is extremely variable. There is very little data concerning the posterior chords, but for the anterior chords average length and thickness are ∼2 cm and 1–2 mm, respectively. Similar to the leaflets, the chords have the ability to adapt, and lengthen in response to altered loading conditions (21).

Papillary Muscles

The lateral and medial PM are categorized based on their relationship to the mitral commissures. The bodies of PM stem from the apical one-third of the LV wall. The Chords emanate from the PM tips to the corresponding anterior, posterior, and commissural leaflet (**Figure 2**). The lateral PM usually has a single head. However, it has a dual blood supply from the left circumflex and left anterior descending artery. On the other hand, the medial PM usually has two heads and is either supplied by the right or circumflex coronary artery (12). PM contraction aims to control the distance between the mitral annulus and the PM tips. On one hand, early during systole longitudinal contraction of the LV base moves the entire PM (base and tip) closer to the annulus. On the other hand, later during systole, isolated PM contraction shortens the length of the papillary muscles, and increases the distance between the PM tip and the annulus. During the first half of systole papillary muscles move closer together and move concurrently toward the mitral annulus due to unopposed longitudinal contraction of the LV base. Because the mitral leaflets moves upwards toward the atrium at the same time this papillary muscle coordinated and symmetric motion, maintains equal distances between the papillary muscle tips and

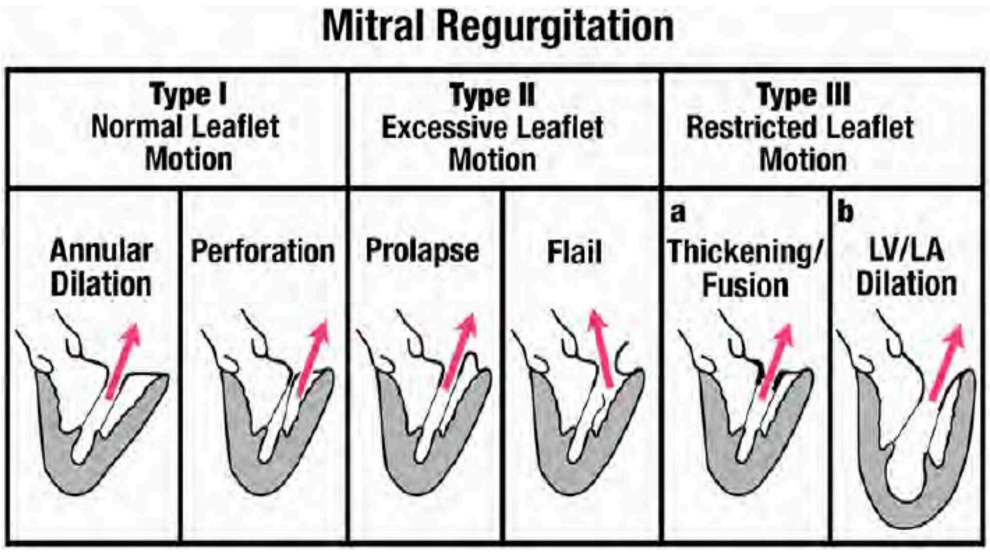

FIGURE 3 | Depiction of mechansims of MR based on the Carpentier classification. From Zoghbi et al. Recommendations for noninvasive evaluation of native valvular regurgitation, A report from the American Society of Echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. Journal of the American society of echocardiography April 2017; 304–363; with permission (33).

leaflets, avoiding distortion of mitral leaflets. Furthermore, at the same time annular contraction and folding occurs allowing early systolic co-aptation by the early saddle-shape accentuation. At the mid and late systolic period the PM bodies contract, and PM tip are pulled downwardly, away from the annulus and closing leaflets, keeping both leaflets under directed tension and posterior restrain to prevent systolic anterior motion of the leaflets, and to avoid left ventricular outflow tract obstruction by the sail-like anterior leaflet.

Pathophysiology of MR

The basic mechanisms for MR were described by Carpentier and are based on the mobility of the leaflets (**Figure 3**). Type I MR involves normal mobility of leaflets with poor co-aptation due to annular dilation or perforation of a leaflet. Classic etiologies associated with the first mechanism (annular dilatation) are MR due to enlarged left atrium usually associated with chronic atrial fibrillation. Etiologies associated with the second mechanism (leaflet perforation) include endocarditis, iatrogenic trauma, or congenital disease. Type II MR involves excessive mobility (prolapse or ruptured chordae) of the leaflets. The classic etiologies associated with these mechanisms are mitral valve prolapse for the first, and fibro-elastic deficiency for the latter. The third mechanism (Type III) is associated with attenuated mobility of leaflets, resulting in co-aptation of leaflets in the ventricular level. This attenuated mobility can be diastolic and systolic (Type IIIa) or just systolic (Type IIIb). The first type (Type IIIa) is secondary to shrinkage of leaflets and/or chords due to inflammatory or congenital disease. Classic etiologies associated with this mechanism are rheumatic heart disease, Carcinoid, or radiation induced MR. In Type IIIb the attenuated mobility is entirely systolic and is always associated with LV enlargement, displacement of papillary muscles away from the mitral annulus, and systolic tethering of mitral leaflets transferred through the tensed chordae tendineae.

Type I MR

Type I MR involves normal mobility of leaflets with poor co-aptation due to annular dilation or perforation of a leaflet. In this review we will focus on Type I functional MR due to pure annular dilatation because it is the most puzzling and poorly understood of all types. Usually, mitral annular dilatation does not result in significant MR because it is counterbalanced by the fact that LV papillary muscles provide chords to both MV leaflets and "hold them together." Furthermore, in the context of AF, the better-developed fibrous skeleton of the mitral annulus rarely advances to severe dilatation compared with the less developed and thinner tricuspid annulus. Thus, severe tricuspid regurgitation is much more common than severe MR in patients with atrial fibrillation (23). However, when massive atrial enlargement occurs, usually due to chronic prolonged atrial fibrillation, the resulting extensive annular dilatation may overwhelm these protective mechanisms and may result in severe functional MR without systolic restrictive motion and tethering of leaflets. By studying follow-up echocardiograms after AF ablation, Gertz et al. (24) evaluated the pathophysiological mechanisms underlying "pure" annular dilatation secondary to atrial fibrillation resulting in functional Type I MR. They showed that patients with successful ablations experienced significant reductions in LA size and mitral annular dimension, and only less than a third still had still significant MR at follow-up. In contrast, among patients who had recurrence of AF, there was no significant change in annular dimension despite reductions in LA size. Over 80% of the patients with recurrence still had

significant MR at follow-up. Their findings showed that mitral annular dimension was the only independent echocardiographic predictor of MR. Another possible mechanism for development of MR in patients with atrial fibrillation involves the loss of LA function. Well-timed atrial contraction at end diastole is followed by atrial relaxation which may "suck in" the mitral leaflets and be important for appropriate mitral valve closing (25). In patients with atrial fibrillation there is neither atrial contraction, nor atrial relaxation, thus the atrial mechanism for mitral closure is lost. In patients with Type I functional MR the LV is generally not significantly dilated and LV systolic function appears normal. This type of MR occurs mostly in elderly patients (∼80 years old). Recently, a group from Japan tried to clarify the mitral geometric changes in patients with atrial functional MR using 3D echocardiography (26). They described the following changes: (1) LA dilatation; (2) MA dilatation; (3) the LV basal posterior wall was bent inward; (4) the anterior mitral leaflet was flattened along the mitral annular plane; and (5) the posterior mitral leaflet was bent toward the LV cavity (**Figure 5**). The authors postulated that the posterior leaflets bending seen in the patients with Type I MR due to LA dilatation had the same mechanism previously described in patients with giant LA due to mitral stenosis. In patients with giant LA, the posterior wall of the LA extends behind the basal posterior wall of the LV. The backward LA enlargement leads to the inward bending of the basal posterior LV, and the tip of the posterior leaflet is tethered to the posterior LV by the papillary muscles and its chords. This atriogenic tethering of the posterior leaflet results in a reduction of co-aptation and worsening MR (**Figure 4**).

Many unresolved questions remain in this type of MR: Is it associated with excess mortality despite normal LV systolic function?: Will it l improve with simple annuloplasty or mitral replacement?: What is the reason for LA dilatation in patients in sinus rhythm?; And should we treat moderate MR when the patients require tricuspid surgery for severe regurgitation due to right-sided annular enlargement secondary to chronic atrial fibrillation. It seems imperative to focus future research on all these questions before we start implanting devices without understanding what it is we treat and what is the degree of benefit.

Type II MR

Type II MR involves excessive mobility (prolapse or ruptured chordae) of the leaflets which can affect one or both leaflets and one or multiple scallops. Two different phenotypes are described: fibroelastic deficiency (FED) and myxomatous disease (also called Barlow disease). FED is mostly localized to one segment, involves ruptured chords with leaflet redundancy and thickening mostly only on the flail segment (usually posterior, especially P2). Usually the remainder of the valve is thin and normal. Conversely, myxomatous disease (MD) usually shows generalized redundancy and thickening of both leaflets, involving multiple segments (**Figure 3**). In MD, MR is typically mostly in mid late systole while it is usually holo-systolic in FED. It is still uncertain whether these diseases are variants along a single pathophysiologic spectrum but recent data showing distinct physiological differences suggests that FED and MD are related but separate entities.

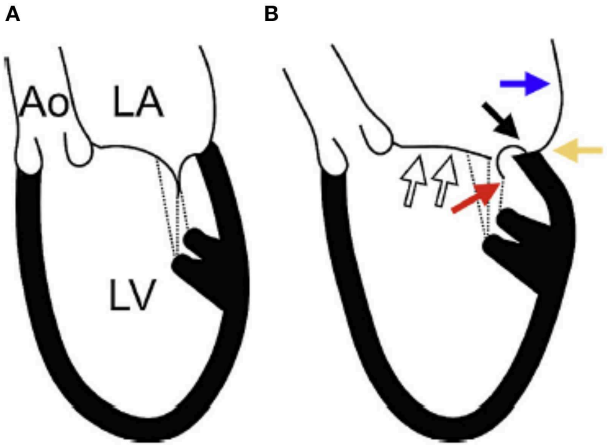

FIGURE 4 | The etiology of atrial functional MR. **(A)** Schematic representation of a normal heart. **(B)** Schematic representation of a heart with Type I functional MR as demonstrated in patients with atrial fibrillation. (White arrows): the anterior mitral leaflet is flattened along the mitral annular plane with left atrial (LA) dilation and associated mitral annular dilation. (Blue arrow): the posterior wall of the LA extends behind the posterior mitral annulus due to LA dilation. (Black arrow): the posterior mitral annulus is displaced backward and upwards to the LA side from the crest of the posterior left ventricle (LV). (Yellow arrow): LA enlargement leads to the inward bending of the basal posterior LV. (Red arrow): the tip of the posterior mitral leaflet is tethered toward the posterior LV by the papillary muscles and the chordae tendineae. As a result, the posterior mitral leaflet curves, and its movement becomes restricted. Ao, ascending aorta; LA, left atrium; LV, left ventricle. From Ito et al. (26) Mechanism of atrial functional mitral regurgitation in patients with atrial fibrillation: A study using three-dimensional transesophageal echocardiography. Journal of Cardiology 70 (2017) 584–590 with permission.

Mitral Annulus Dynamics

MA in patients with MD is enlarged, flattened, and more circular, with increased anteroposterior diameter, inter-commissural diameter, circumference, and area compared with normal valves. On the other side, annulus height is close to normal. Annular enlargement is correlated with severity of MR (27, 28). Importantly, annular enlargement in patients with MD is different from that of patients with ischemic MR, in which only the anteroposterior annulus is enlarged. In Type II MR there is also marked inter-commissural enlargement, suggesting that annular enlargement is an intrinsic part of the disease (1, 29).

The dynamics of Type II MR annular are controversial. In some studies (4) normal annular dynamics have been described.

Conversely, we and others (28, 29) observed abnormal early-systolic annular dynamics in patients with Type II MR. These patients had reduced anteroposterior contraction combined with simultaneous enlargement of inter-commissural diameter resulting in diminished annular area contraction. Systolic saddle shape accentuation was delayed and attenuated. Because early systolic saddle shape accentuation seems to play a role in avoiding early systolic regurgitation, these abnormalities can result in the addition of an early-systolic regurgitation component in patients with mitral prolapse and may lead to severe holo-systolic regurgitation. Furthermore, in late systole the annulus increases in area instead of the normal decrease, which may

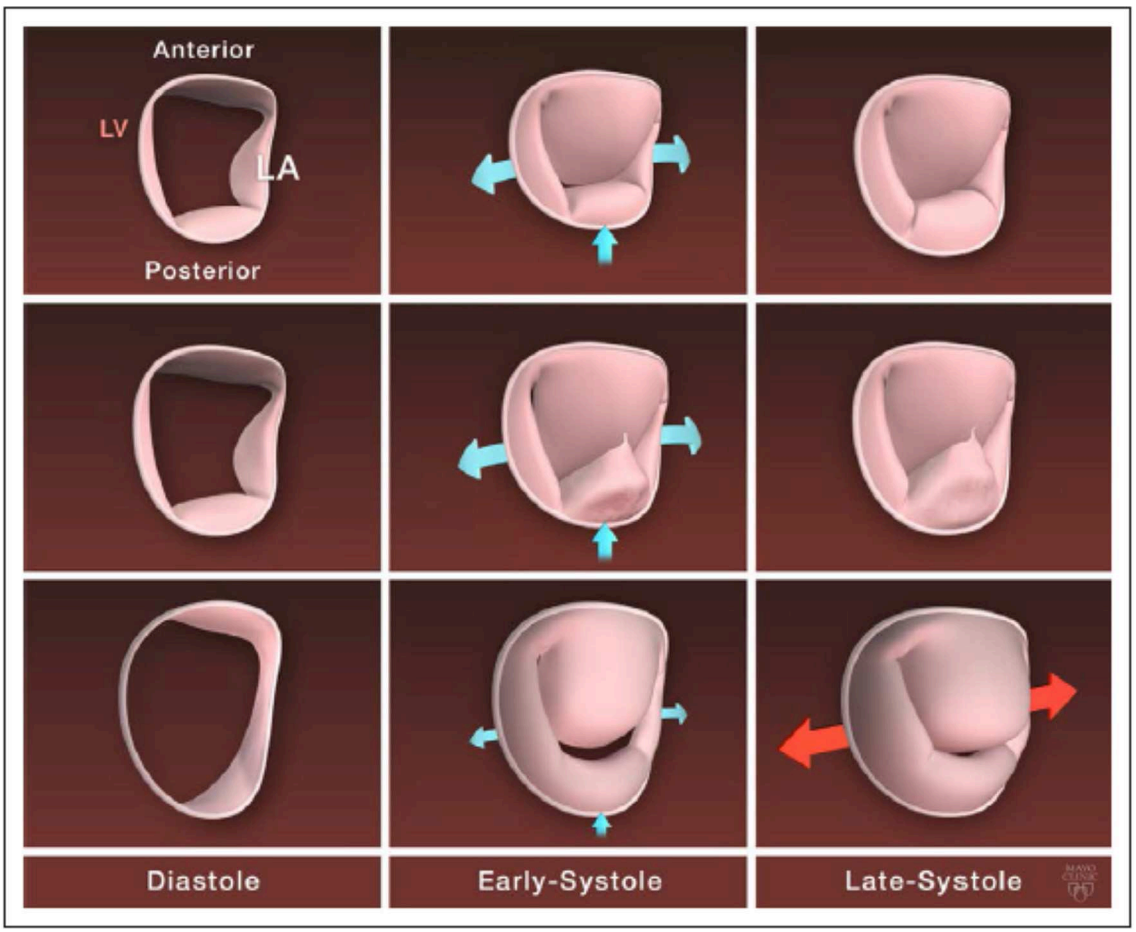

FIGURE 5 | Mitral annulus dynamic in normal mitral valve and by degenerative mitral regurgitation phenotype. Top row, Normal mitral annulus dynamic with stretching of the commissure toward the ventricle and anteroposterior contraction in early systole and few modification in late systole. Middle row, Mitral annulus dynamic in fibroelastic deficiency: moderately enlarged dynamic with similar motion in early systole but of decreased magnitude compared with normal annulus. Bottom row, Mitral annulus dynamic in diffuse myxomatous disease with a severely enlarged and flattened mitral annulus, a severe decrease in the anteroposterior contraction in early systole, and an abnormal enlargement of the intercommissural diameter in late systole. LA indicates left atrial; and LV, left ventricle. From Antoine et al. (34) pathophysiology of degenerative mitral regurgitation. Circulation: cardiovascular imaging. 2018; 11 with permission.

contribute to further separation of late systolic mitral leaflets and accentuation of the late systolic component of MR (**Figure 5** and **Supplementary Movies 2A,B**). Some differences between annular dynamics in patients with FED vs. MD raise the question if Type II MR should be seen as a single entity or as different dynamic phenotypes (30). For similar MR severity and left ventricle, or left atrium dimensions, the annulus in patients with MD was larger, flatter, and with more inter-commissural enlargement than in patients with FED (**Figure 5**). This exaggerated annular enlargement in patients with MD was unexplained by LV or LA remodeling, or by the severity of regurgitation suggesting that it is an intrinsic part of the disease and not just secondary to MR or its consequences. On the other side, in patients with FED annular motion and dimensions were close to normal (**Figure 5**) and correlated with MR severity. In conclusion, it seems that in patients with Barlow's disease annular dynamics are extremely abnormal as an intrinsic part of the disease and play a significant role in perpetuating MR. On the other side, in FED the primary disease is of leaflets and annular dysfunction and dilatation is just secondary to MR.

Leaflet in Type II MR

Leaflet redundancy could not be quantified until new 3D echo technology allowed direct measurement of leaflets' areas. Recent reports have shown that in patients with Type II MR leaflet tissue area is increased vs. controls. Furthermore, prolapse volume and height were correlated with the severity of MR (27, 31). Interestingly, for similar severity of MR, leaflet redundancy is larger in MD vs. FED (31). Importantly, dynamic differences between patients with MD and FED were even more remarkable. In patients with MD larger dynamic increase of prolapse volume was seen compared to patients with FED. In patients with FED leaflets' areas remain stable throughout the cardiac cycle. However, in MD leaflet's prolapse volume and height increases in late systole. This suggests that there is very little valvular tissue reserve in FED compared to substantial tissue reserve available

to expand during systole in MD (30). **Figure 5** summarizes the differences between FED and MD phenotypes of Type II MR from static and dynamic perspectives.

Type III MR

The third mechanism (Type III) for MR is associated with decreased mobility of leaflets, resulting in co-aptation of leaflets in the ventricular level (**Figure 3**). This attenuated mobility can be diastolic and systolic (Type IIIa) due to organic shrinkage of leaflets and /or chords, or just systolic (Type IIIb). In this review we will focus on Type IIIb MR due to systolic restricted movement of leaflets secondary to LV systolic dysfunction and adverse remodeling.

Type IIIb functional MR occurs despite structurally normal mitral leaflets as a consequence of LV dysfunction. It is unquestionably associated with LV remodeling and enlargement. It has been attributed to global LV dilatation, mitral annulus enlargement, or local LV remodeling associated with apical and posterior displacement of papillary muscles leading to excess valvular tenting (32).

Recent advances in 3D Doppler echocardiography allow assessment of regurgitant flow throughout the cardiac cycle. These advances permit new insights into the pathologic dynamics of the mitral annulus, and papillary muscle movement (1).

Mitral Annulus Dynamics in Type III MR

Compared with control subjects, the annulus in patients with Type IIIb MR is larger throughout the cardiac cycle. We have recently shown that although inter-commissural diameter was similar in all patients with low ejection fraction (EF) with or without MR, patients with Type IIIb MR have a larger antero-posterior diameter compared to patients with systolic dysfunction but no MR. Furthermore, not only baseline annular geometry was different, but also annular dynamics were pathologic in patients with Type IIIb MR. In these patients early systolic annular folding, and saddle-shape deepening was absent. In fact in patients with significant Type IIIb MR an adynamic annulus in terms of saddle shape was observed.

In conclusion, the loss of annular folding across the inter-commissural axis and the loss of saddle shape accentuation in early systole, plays a role in early-systolic Type IIIb MR just as it is in myxomatous mitral valve disease (1).

Papillary Muscles Type IIIb MR

In patients with low EF, irrespective of MR severity, inter-papillary muscle approximation is attenuated. This is possibly due to reduced circumferential and radial basal contraction. On the other hand, there are marked differences between patients with and without FMR, in terms of papillary muscle movement toward the mitral annulus. In patients with low EF but no MR papillary muscle to mitral annulus approximation is suppressed compared to control patients, but the distances between the two muscles and the annulus remain equal and symmetric, avoiding excessive mid-systolic tethering and distortion of mitral leaflets. In contrast, in patients with Type IIIb MR postero-medial muscle tip tends to paradoxically move away from the annulus during mid systole. Thus, as opposed to the normal valve, irrespective of EF, in which firm apposition of the leaflets by intra-ventricular pressure is assisted by the symmetric descent of papillary muscles toward the annulus, in patients with Type IIIb MR, asymmetric mid-systolic papillary muscle displacement results in abnormal tethering geometry (1).

In conclusion, as opposed to early-systole, in which annular folding plays a critical role, in the second and third parts of systole, asymmetric papillary muscle motion toward the annulus is the main determinant of late systolic MR.

Subgroup Analysis

Analysis of the mechanism of MR in patients with anterior MI, global dysfunction and inferior MI shows that those mechanisms differ depending on the etiology of LV dysfunction (1). In patients with anterior MI and/or global dysfunction the loss of normal deepening of saddle shape contributes significantly to worse early systolic MR, but it is less important in patients with inferior MI. On the other hand, in patients with inferior MI early systolic MR depends entirely on tenting volume. On the other hand, in mid-systole MR depends only on annular area in patients with anterior MI, but on symmetry and coordination of papillary muscle motion in both inferior MI and global dysfunction patients.

Mitral Valve Repair

Mitral valve repair has become the procedure of choice in patients with functional MR because of its advantages over valve replacement regarding long-term survival and freedom from valve-related adverse events. In the early seventies Carpentier initiated the modern era of mitral valve repair (35). Since then the repair techniques have continued to evolve with the improved understanding of the structure and dynamics of the mitral valve. In this paragraph we will briefly summarize the standard surgical corrections for the most common mechanisms of MR.

Type II MR

The most common mechanism of MR needing mitral repair is Type II MR. Carpentier was the first to introduce the quadrangular resection technique, which became the first standard to treat posterior leaflet prolapse (35). In this technique the first step is to identify the prolapsing segment of the mitral leaflet and excise it with its associated ruptured or elongated chordae from the free margin of the leaflet down to the annulus. In the second step annular plication is performed to reduce the orifice size. The repair is completed by an annuloplasty band or ring. In the following years the triangular resection technique was developed to simplify the operation and reduce the risk of complications by eliminating the need for annular plication (36). This technique is ideal for patients with segmental posterior leaflet prolapse but can also be used in isolated anterior prolapse involving a small segment as well. To avoid systolic anterior motion (SAM) the "sliding plasty" technique was added to reduce the height of the posterior leaflet to prevent SAM. This technique is useful mostly for patients with Barlow's disease or in cases with excess leaflet tissue of the prolapsing posterior segment (35). Since then numerous other techniques to avoid SAM have been introduced. Although resection techniques are associated with favorable outcomes, they have some drawbacks including reduction of leaflet tissue, which

is the major component of the surface of coaptation and the need for annulus plication that may deform of the sub annular region of the left ventricle resulting in injury to circumflex artery or SAM. Frater and David introduced the use of artificial chordae to replace elongated or ruptured chordae responsible for mitral valve prolapse and mitral regurgitation (37, 38). These neo-chordae used polytetrafluoroethylene (PTFE) sutures, usually made of Gore-Tex. The neo-chordae eliminate prolapse by supporting the free edge of the leaflet and thereby produce an optimal surface of coaptation. Usually the PTFE suture is passed through the fibrous region of a papillary muscle on the same side of the valve as the region of prolapse. Each end of the suture is brought up to the leaflet edge and passed through the leaflet tissue in the region of prolapse. In the final stage the chordal length is adjusted to a level to prevent prolapse and the suture is tied on the atrial side of the leaflet (37, 38). Another common technique, the edge to edge repair was introduced by Alfieri et al. in the early nineties. This technique is especially useful for correction of isolated anterior leaflet prolapse or bileaflet prolapse due to Barlow's disease. This approach involves anchoring the free edge of the prolapsing leaflet to the corresponding free edge of the opposite leaflet, resulting in a double orifice valve. An annuloplasty completes the repair (39). Due to the risk of inducing stenosis, the edge-to-edge repair is not recommended in patients with a small mitral valve area. Furthermore, results are sub-optimal when an annuloplasty is not included. Finally, poor results after anterior leaflet resection led to a variety of repair methods including chordal transfer, chordal shortening and artificial chordal replacement. Because the use of neochordae has been associated with improved results as compared to chordal transfer, it is currently the procedure of choice to correct anterior leaflet prolapse (37, 38).

Type IIIb MR

After Type II MR, Type IIIb is the most common mechanism for mitral valve repair. Mitral valve repair with a restrictive annuloplasty has been the treatment of choice to address Type IIIb MR for many years. It restores leaflet coaptation by decreasing the anteroposterior distance and the valve area (40). The annuloplasty is performed with a complete and rigid ring at least one or two sizes smaller than the size necessary to improve leaflet coaptation. In some cases LV remodeling may continue after repair resulting in further displacement of the papillary muscles worsening tethering and recurrence of MR. Because the rate of MR recurrence after restrictive annuloplasty may reach 10–20% rates early after operation and up to 50–70% at 5 years multiple annuloplasty rings have been designed to address the changes in annular shape associated with Type IIIb MR. However, there are no studies that prove their superiority. Other adjuvant techniques, include division of secondary chordae, placement of edge to edge stitches, and reposition of papillary muscles, have been promoted to decrease the rate of recurrence (40). However, long term results and indications for those techniques are still lacking.

Type I MR

Type I functional MR is rare and is usually repaired by annuloplasty. A number of annuloplasty devices are available and include complete (rings) or partial (bands), and may be rigid, semi-rigid or flexible. Currently there is no consensus regarding the selction of annuloplasty device.

While surgery remains the mainstay for treatment in MR, several technological advances in the last years have made trans-catheter mitral valve interventions feasible and safe. The use of these techniques in patients with severe MR has shown promise in reducing symptoms, improving quality of life, with potential for a survival advantage among certain patients with secondary MR. The most commonly used device is the MitralClip (Abbott Laboratories, Menlo Park, California, USA), a cobalt chromium clip covered that has two arms and works by grasping and approximating edges of the anterior and posterior valvular leaflet segments. The MitralClip was designed after the surgical Alfieri technique and received CE-Mark and FDA approval for use in primary Type II MR and functional Type I and IIIb MR. Another similar device is the PASCAL TMVR (Edwards Lifesciences, Irvine, CA). Other devices include the indirect annuloplasty devices such as the Carillon system, ARTO device, Mitral Loop Cerclage Catheter System, and the direct annuloplasty devices such as the Cardioband (Edwards Lifesciences, Irvine, CA), Mitralign system (Mitralign, Tewksbury, Massachusetts) and the Millipede IRIS ring, all imitating surgical annuloplasty and designed to treat functional Type I and IIIb MR.

CONCLUSIONS

MR is affected by a complex dynamic change of the annulus, leaflets, chords, papillary muscles, and atrial and ventricular interaction. It is associated with different mechanism depending of the Type of MR. In patients with Type I MR it is linked mostly to annular and left atrial factors. In patients with Type II MR, the major contributors are related to annular and leaflets factors. In Type IIIb MR the major contributors are tenting volume, loss of annular contraction across the inter-commissural axis (annular folding), and to asymmetric papillary muscle dynamic changes that are linked to the valve deformation. These new insights should lead to refined concepts for MR pathophysiology and repair techniques.

SUMMARY

In this review we describe the anatomy and physiology of the different parts of the mitral valve apparatus including the annulus, leaflets, chordae tendineae and papillary muscles in normal subjects and with different types of mitral regurgitation (MR). We show that MR is affected by a complex dynamic change of all the components of the apparatus and their interactions. Furthermore, different types of MR are associated with different mechanisms and pathologic interactions. Type I MR it is linked mostly to annular and left atrial factors, Type II MR is related mostly to annular and leaflets factors but in Type IIIb the major contributors are tethering of leaflets, loss of annular folding, and asymmetric papillary muscle dynamic changes that are linked to the valve deformation. These new insights should lead to refined concepts for MR pathophysiology and repair techniques.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2020.00084/full#supplementary-material

Supplementary Movie 1 | Schematic representation of a 3D reconstructed normal mitral annulus and leaflets in motion. Note that in early-systole anteroposterior folding across the fixed inter-commissural diameter occurs, leading to early-systolic annular area contraction, accentuation of saddle shape, and approximation of anterior, and posterior leaflets. This annular contractions results in leaflet approximation when systolic ventricular pressure is still relatively low and does not yet press the leaflets together and may be important in preventing early systolic mitral regurgitation.

Supplementary Movie 2 | (A,B) Schematic representation of a 3D reconstructed mitral annulus and leaflets (oblique view **A**; En face **B**) in motion in a patient with Type II MR compared to normal valve. Note that in normal valve the mitral annulus is dynamic with anteroposterior contraction and accentuation of saddle shape in early systole. On the other hand, the mitral annulus in myxomatous disease is severely enlarged and flattened and has an attenuated anteroposterior contraction in early systole, and an abnormal enlargement of the inter-commissural diameter in late systole.

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