

Transcatheter mitral valve repair: review of the clinical evidence



Maurizio Taramasso^{1*}, MD, PhD; Ted Feldman², MD; Francesco Maisano¹, MD, PhD

1. University Hospital of Zurich, University of Zurich, Zurich, Switzerland; 2. Evanston Hospital, Evanston, IL, USA

KEYWORDS

- mitral regurgitation
- mitral valve
- transcatheter mitral repair

Abstract

Over the past decade, different transcatheter repair techniques have been developed to treat mitral regurgitation (MR) with less invasive approaches in order to address the unmet clinical need of untreated patients with MR. The aim of this report is to provide an overview of the currently available transcatheter mitral repair options, focusing on the evidence reported so far.

*Corresponding author: Heart Valve Clinic, University Hospital of Zurich, University of Zurich, Raemistrasse 100, 8060 Zurich, Switzerland. E-mail: maurizio.taramasso@usz.ch

Abbreviations

DMR	degenerative mitral regurgitation
FMR	functional mitral regurgitation
LV	left ventricle
MR	mitral regurgitation
MVARC	Mitral Valve Academic Research Consortium
TMVI	transcatheter mitral valve implantation

Introduction

THE CLINICAL PROBLEM

Mitral regurgitation (MR) is a common entity which affects about 10% of individuals over 75 years of age in the general population¹. The natural history of severe MR is unfavourable, leading to worsening LV failure, pulmonary hypertension, atrial fibrillation, and death². The most common aetiology of primary MR in Western countries is degenerative MR (DMR), due to leaflet tissue alteration and degeneration, leading to mitral valve (MV) prolapse or flail³.

On the other hand, secondary or functional MR (FMR) is the consequence of left ventricular (LV) dysfunction and dilation, usually due to post-ischaemic or idiopathic dilated cardiomyopathy, leading to secondary MR⁴ due to annular dilatation and leaflet tethering, which prevent proper closure of the valve in spite of anatomically normal valve leaflets⁵.

Open heart surgery is the gold standard for the treatment of severe DMR as excellent outcomes can be achieved in most patients, often adopting minimally invasive approaches⁶.

In severe DMR in particular, surgical repair represents the optimal treatment. If performed before the onset of limiting symptoms, atrial fibrillation or development of LV dysfunction, MV repair is able to restore normal life expectancy and quality of life⁷. By contrast, surgical correction of functional FMR is controversial, since the prognosis is more related to the cardiomyopathic process than to MR itself. Outcomes after surgical correction of FMR remain suboptimal, recurrence of MR is frequent, and peri-operative mortality is not negligible⁸⁻¹⁰.

Nevertheless, the vast majority of patients with MR do not undergo surgical treatment. The Euro Heart Survey conducted by the European Society of Cardiology (ESC) showed that up to 50% of patients with severe MR are denied surgical treatment because they are felt to be at too high risk for surgery owing to advanced age or comorbidities¹¹. Other common reasons are a combination of limited local access to surgeons with expertise, general reluctance for an open procedure, or a lack of perceived survival benefit, especially in FMR^{12,13}.

Therefore, over the past decade, different transcatheter techniques have been developed to treat MR with less invasive approaches, in order to address the unmet clinical need of untreated patients with MR. The field of percutaneous MR treatment is highly active, with several technologies being actively developed (including repair and replacement technologies) and some of the repair devices being already commercially available¹⁴.

The aim of this particular report is to provide an overview of the currently available transcatheter mitral repair options,

focusing on the (little) evidence reported so far. **Table 1** shows the randomised trials currently recruiting in the field of transcatheter mitral valve repair.

Table 1. Ongoing randomised trials with transcatheter mitral repair therapies.

Name of the study	Device group	Control group
Degenerative MR		
Mitra-HR	MitraClip	Surgery
RECHORD	NeoChord	Surgery
Functional MR		
COAPT	MitraClip	GDMT
RESHAPE-HF2	MitraClip	GDMT
MITRA-FR	MitraClip	GDMT
MATTERHORN	MitraClip	Surgery
ACTIVE	Cardioband	GDMT
REDUCE-FMR	Carillon	GDMT
GDMT: guideline-directed medical therapy		

THE COMPLEXITY OF THE MITRAL VALVE APPARATUS

From the beginning, it was clear to all physicians approaching the field of transcatheter MV treatment that addressing the MV would be associated with technical challenges and anatomical complexity in a totally different way compared to those of the aortic valve field¹⁵.

The MV is a complex apparatus integrated in the LV, including the annulus, the leaflets, the chordae, the papillary muscles, and the ventricle itself. Beyond its haemodynamic function to ensure forward cardiac output, the mitral apparatus plays a fundamental role in the structural and functional integrity of the LV; the discontinuation of this integrity is associated with worsening LV performance.

Abnormalities of any part of the MV complex (leaflets, annulus, chordae tendineae, and papillary muscles) or the LV can lead to MR. Not infrequently more than one component of the complex is affected. This represents a major challenge in terms of percutaneous repair, since it may be necessary for a single operator to master different techniques if a complete repair is the aim¹⁶.

The complexity of the subvalvular apparatus and the distribution of chordae tendineae increase the risk of damage or entrapment with all of the leaflet repair devices (**Figure 1**). The mitral annulus is a 3D saddle shape and a highly movable structure, which usually loses its 3D configuration and contractility in diseased valves. Different vital structures are in proximity to the mitral annulus, such as the coronary sinus and left circumflex artery, and thus are vulnerable to impingement by some devices.

TRANSCATHETER MITRAL VALVE REPAIR

As discussed above, the variety of different pathological mechanisms underlying MR and the complex anatomy of the mitral valve have led to the development of different technologies, each

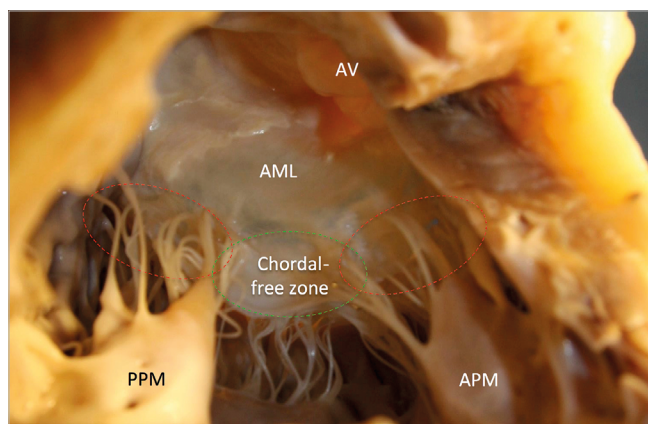


Figure 1. View of the mitral valve apparatus from the LV. In this anatomical cut, the right ventricle and the interventricular septum have been removed in order to show the subvalvular apparatus of the MV and the distribution of the chordae tendineae. Each papillary muscle provides chordae for the anterior and posterior mitral valve leaflet. The green ellipse marks the “chordal-free zone”, which corresponds to the A2-P2 region (middle part of the mitral valve), where the risk of chordal impingement is minimal. The red ellipses show the regions corresponding to the lateral (A1-P1) and the medial (A3-P3) regions, where the risk of chordal impingement is higher: Chordal density is maximal in the commissural zones. AML: anterior mitral leaflet; APM: anterolateral papillary muscle; AV: aortic valve; PPM: posteromedial papillary muscle

of them focused on the treatment of a specific anatomical lesion or component of the valve apparatus.

The latest 2017 European Society of Cardiology guidelines reflect the lack of evidence produced so far in order to support

the clinical use of transcatheter mitral repair methods. In fact, the only recommendation for any transcatheter repair is a class IIb recommendation for transcatheter edge-to-edge repair, which may be considered in inoperable or high-risk patients with symptomatic severe MR, avoiding futility in this patient group with many comorbidities. However, it is interesting to note that this recommendation shares the same level of evidence (IIb) as mitral surgery in the context of isolated FMR, reflecting the paucity of evidence for surgical repair in this setting also^{17,18}.

Transcatheter MV repair devices are conventionally classified into three groups: leaflet devices (including chordal repair), annuloplasty repair devices, and LV remodelling devices, according to the therapeutic target. To complete the portfolio of transcatheter mitral therapy, transcatheter mitral valve implantation (TMVI) is rapidly emerging (**Figure 2, Figure 3**).

LEAFLET DEVICES

MITRACLIP® (ABBOTT VASCULAR, SANTA CLARA, CA, USA)

MitraClip implantation is the most widely available percutaneous therapy for native MR, with more than 60,000 patients treated worldwide so far. The main advantages of the MitraClip device are its versatility (since it has been successfully used in both degenerative and functional aetiologies and in different clinical settings) and its safety, which has been shown even in extreme risk heart failure patients¹⁹⁻²³. Using a 24 Fr transvenous, transseptal system, one or more clips are used to approximate the free edges of the anterior and posterior leaflets, replicating by a percutaneous approach the so-called Alfieri edge-to-edge surgical mitral repair technique. The safety profile of MitraClip therapy is excellent. The in-hospital mortality rate reported in different series, including high-risk and inoperable patients and often including

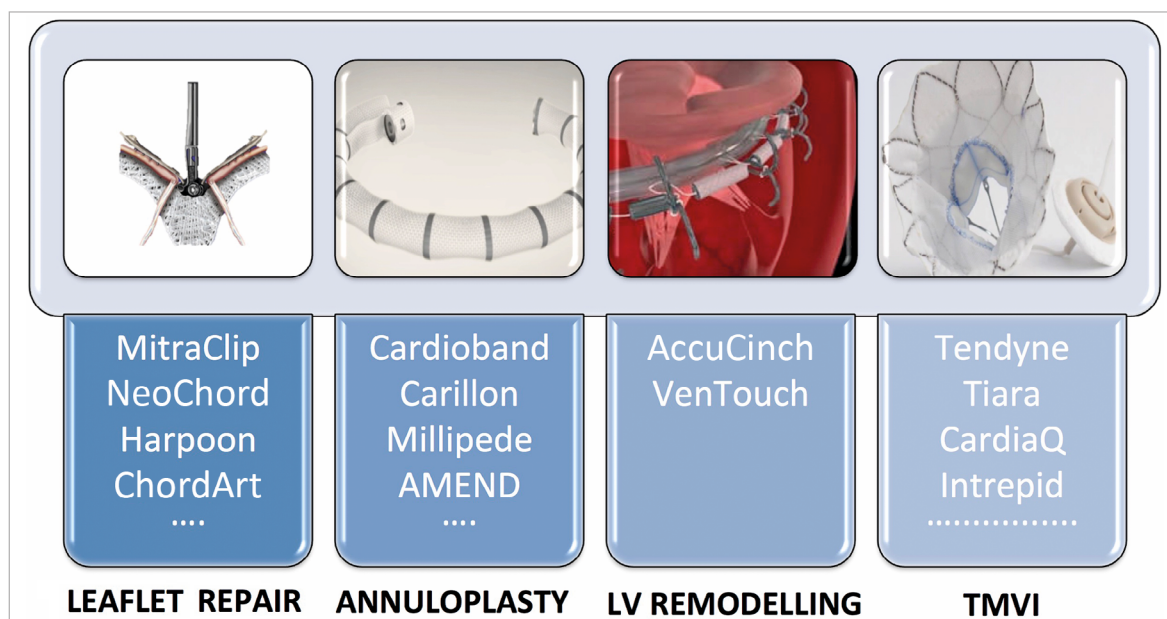


Figure 2. Classification of transcatheter mitral valve therapies according to the therapeutic target. TMVI: transcatheter mitral valve implantation

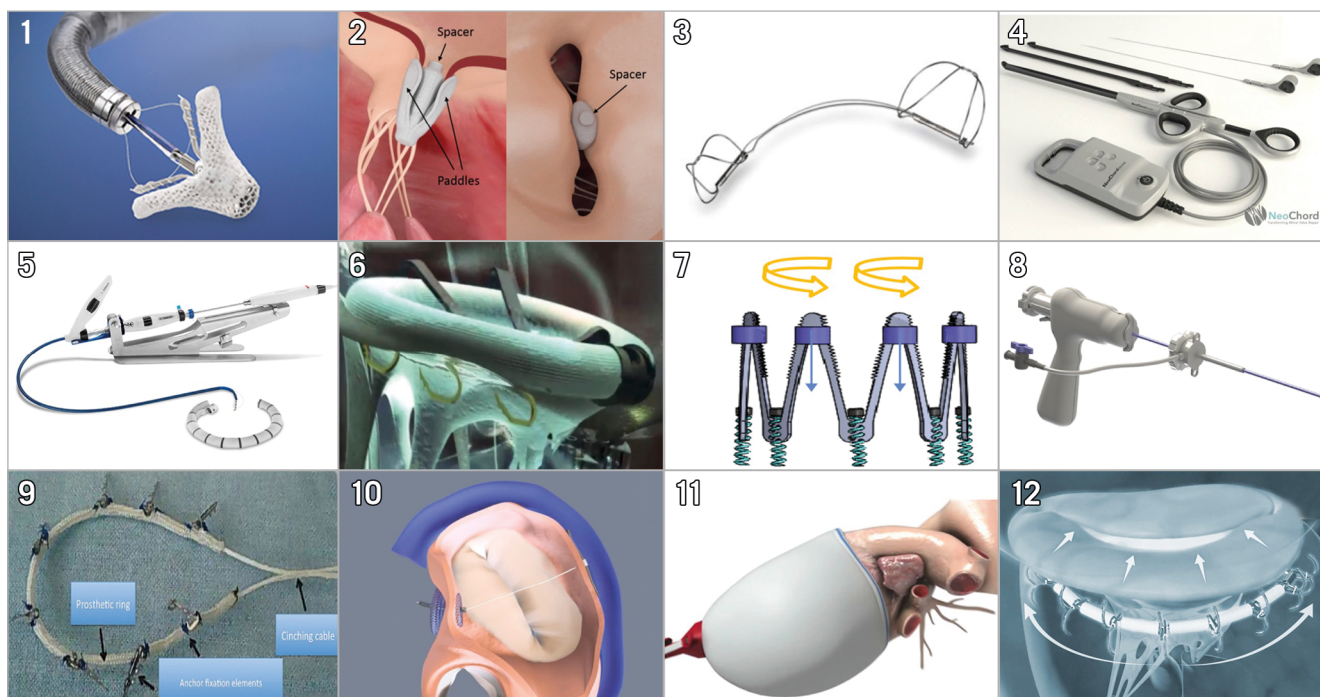


Figure 3. Transcatheter mitral valve repair devices. 1) MitraClip. 2) PASCAL. 3) Carillon. 4) NeoChord. 5) Cardioband. 6) AMEND. 7) Millipede. 8) Harpoon. 9) Carillon® Mitral Contour System. 10) ARTO. 11) VenTouch. 12) AccuCinch.

data from low-volume centres participating in the registries, is about 2-3%; the morbidity rate is also low. The duration of hospital stay in many series is less than three days. The rate of single leaflet detachment is low, now being 1-2%, while clip embolisation remains extremely rare^{13,19,20,22,24}.

In terms of efficacy, procedural success (reduction in MR to $\leq 2+$) occurs in about 90% of selected patients, with about 65% of patients having residual MR $\leq 1+$ ^{19-21,23}. Despite the improvement in intraprocedural imaging and patient selection, there is still a non-negligible proportion of patients with residual or recurrent significant MR. Limited information is available so far concerning the long-term durability of MitraClip therapy, especially in patients with a functional aetiology²⁵.

Final five-year results of the randomised EVEREST II trial showed that MitraClip therapy was less effective in reducing MR than open surgical repair in standard surgical candidates, mainly with DMR²⁶. Currently, the MitraClip is approved for treatment of high-risk patients in Europe (primary or secondary MR) and in the USA (primary MR only), with a class IIb recommendation^{17,18}.

Despite current European guidelines recommending the use of MitraClip for both functional and primary mitral regurgitation, differences in reimbursement policies across European countries have resulted in different usages (e.g., in France, MitraClip is reimbursed only for primary MR).

A randomised trial in France comparing MitraClip with surgical repair in high-risk but operable patients with DMR has just started enrolment, namely the Mitra-HR trial (ClinicalTrials.gov Identifier: NCT03271762). MitraClip use in real-world clinical practice is

mainly reserved for high-risk candidates with FMR. The acute safety and efficacy results are similar for both aetiologies, although the one-year mortality is, unsurprisingly, higher for FMR patients.

Risk factors for suboptimal outcome and increased mortality after MitraClip therapy include residual or recurrent significant MR $>2+$, severe tricuspid regurgitation or right ventricular dysfunction at baseline, severe pulmonary hypertension and advanced heart failure^{19,22,24,27,28}.

Although symptom improvements, reduction in HF hospitalisation and LV positive reverse remodelling have all been shown after MitraClip treatment, a survival benefit has not been demonstrated as yet. Ongoing randomised trials (COAPT, RESHAPE-HF2 and MITRA-FR) comparing MitraClip and optimal medical therapy will probably address this clinical issue.

The new MitraClip XTR has recently been introduced, with longer clip arms and improved device steerability.

Recently, the potential cost-effectiveness of the MitraClip as compared to surgery or medical therapy has been reported. Feasibility of early discharge after the procedure could potentially contribute further to improving the cost-effectiveness of MitraClip therapy, mainly in heart failure patients²⁹⁻³¹.

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

The PASCAL device (PAddles Spacer Clasps ALfieri) is a new technology to perform transcatheter edge-to-edge mitral repair. Introduced with a 22 Fr steerable system through the transseptal approach, it consists of a 10 mm central spacer that acts as filler in the regurgitant orifice, and is attached to the valve leaflets by

two paddles and clasps. The clasps can be operated either simultaneously or independently to facilitate leaflet capture in complex anatomies.

First-in-man experience in 23 patients with severe MR and thought not to be good anatomic candidates for MitraClip therapy (EuroSCORE II 7.1%, STS score 4.8%) saw the device successfully implanted in all the cases, resulting in a procedural residual MR of grade 2+ or less in 22 (96%) patients. The safety profile was favourable, with only two observed minor periprocedural complications (one minor bleeding event and one transient ischaemic attack). M-VARC technical success was achieved in 22 out of 23 patients (96%), and device success at 30 days was achieved in 18 (78%) patients. Three patients (13%) died during the 30-day follow-up. Significant clinical improvements were observed in the 20 patients alive 30 days after implantation³².

Based on surgical experience, the main limit of both transcatheter edge-to-edge approaches is the absence of annuloplasty, which may affect durability of the repair at long-term follow-up. The use of combined therapy (leaflet+annuloplasty devices) can potentially overcome this limit and provide better durability³³.

NEOCHORD DS1000 (NEOCHORD, ST. LOUIS PARK, MN, USA)

Based on a solid surgical background, catheter-based implantation of the NeoChord is an appealing option to treat DMR. The NeoChord DS1000 is a minimally invasive system that uses adjustable PTFE sutures, through a transapical approach, on the beating heart, to enable support to the free edge of MV leaflets with real-time adjustment of the artificial chordal length for treatment of DMR.

Following the initial results reported in the TACT feasibility trial, with an overall reduction of MR to $\leq 2+$ in 86.7% of 30 patients, the device obtained CE mark in 2012 and has been used in over 500 patients so far³⁴.

The efficacy in reducing MR clearly depends on the complexity of the lesion. In simple anatomy, such as isolated P2 segment flail or prolapse, one-year freedom from a composite endpoint including mortality, MR recurrence, mitral surgery, rehospitalisation and stroke was 94%. In the presence of multiple posterior leaflet segment prolapse/flail or in the presence of a more complex anatomy (bileaflet or commissural involvement), freedom from the composite endpoint was 82% and 63%, respectively. A learning curve effect has also been observed^{35,36}.

In the USA, NeoChord is currently under clinical investigation in the “Randomized trial of the NeoChord DS1000 system versus open surgical repair” (RECHORD). The major limitation of this technology with the current-generation device is the transapical access. The device is delivered sheathless and requires multiple entries and exits through the apex in case of the need for multiple chordae, with a consequent bleeding risk and the challenge of treating multi-segment disease.

HARPOON TSD-5 (EDWARDS LIFESCIENCES)

Recently, the Harpoon device has been investigated in an early feasibility trial in patients with DMR and posterior leaflet

prolapse. The Harpoon system is a 14 Fr device that allows the operator to implant multiple PTFE chordae through the transapical access, on the beating heart, and subsequent live transoesophageal echocardiography (TEE) adjustment of the chordal length. It differs from the NeoChord in terms of its leaflet engaging mechanism (leaflet anchoring with a preformed knot instead of free-edge leaflet fixation) and the use of a smaller introducer sheath on the LV apex which allows easier and repeated access. The fixation of the neochordae far from the free edge of the leaflet may represent a concern in long-term follow-up.

Among the 30 patients reported in the initial feasibility trial, three patients required conversion to open mitral surgery. There were no deaths, strokes, or permanent pacemaker implantations. At one month, MR was mild or less in 89% (24/27) and was moderate in 11% (3/27). At six months, MR was mild or less in 85% (22/26), moderate in 8% (2/26), and severe in 8% (2/26). Favourable cardiac remodelling at six months including decreases in LV and left atrial (LA) volumes, as well as mitral annulus diameter reduction, was observed³⁷.

Patient selection remains the critical point to both chordal implantation devices. So far, the ideal candidate for a successful and durable repair seems to be the patient with a monosegmental DMR, no or mild annular dilatation and limited LV dilatation (due to the risk of recurrent prolapse in case of LV volume reduction). Moreover, differently from surgical chordal repair, the distal extremity of the PTFE suture is not fixed to the papillary muscles, as in the native anatomy, but is fixed to the apical access. The potential consequences of this last aspect at long-term follow-up are unknown.

CHORDART™ (COREMEDIC GMBH, TUBINGEN, GERMANY)

In order to overcome some of the limitations of the two above-mentioned devices, the ChordArt system has been developed to implant pre-measured neochordae by using an antegrade approach (transatrial or transeptal), with a unique and simple method of anchoring the distal chord directly to the papillary muscle (therefore in its anatomical position). The size of the implant can be established on echo or computed tomography (CT) preoperative imaging. The device is completing preclinical validation and FIM implant is planned by Q1 of 2019 (Weber A. Changing the Way of Treating Mitral Valve Prolapse: A Sutureless Neochordal Replacement. TCT 2016, Washington, DC, USA. Available at <https://www.tctmd.com/slide/changing-way-treating-mitral-valve-prolapse-sutureless-neochordal-replacement>).

Similar to the edge-to-edge approach, all the transcatheter chordal repair approaches are carried out without mitral annuloplasty. This could potentially have a negative impact on the long-term durability of the repair.

ANNULOPLASTY DEVICES

Mitral annuloplasty is the most commonly performed technique during conventional mitral surgery, in order to restore the normal ratio between the leaflet surface area and the annular area, to improve leaflet coaptation, and to counteract progressive annular

dilatation that can lead to recurrent MR. Surgical annuloplasty is almost invariably performed in conjunction with leaflet repair in DMR treatment and it is commonly used as stand-alone treatment in selected patients with FMR, in order to force leaflet coaptation using undersized annuloplasty^{38,39}. Suture annuloplasty techniques have almost been abandoned in surgical practice, with the availability of the different ring prostheses that are implanted on the atrial surface of the mitral annulus. A number of prosthetic rings are commercially available, with different features for different anatomical and clinical scenarios (complete versus incomplete rings, flexible versus semi-rigid versus rigid, aetiology-specific rings); however, operator preference and experience is the main factor determining the choice of ring in most cases.

Transcatheter annuloplasty has the potential to serve as a stand-alone therapy in selected patients with FMR with a minimal anatomical and physiological impact, with the advantage, differently from the edge-to-edge devices for example, of keeping the option open for eventual further leaflet treatment or for mitral valve implantation. Moreover, it has the potential to be associated with leaflet repair in order to improve the durability of the repair, or to serve as a future platform for valve-in-ring implantation.

Different percutaneous annuloplasty approaches have been developed to remodel the mitral annulus either indirectly (based on the anatomic proximity of other structures, such as the coronary sinus, to the posterior mitral annulus) or directly, using anchors or sutures to implant the device on the atrial surface of the mitral annulus, to perform either a partial or a complete mitral annuloplasty.

INDIRECT ANNULOPLASTY

CARILLON® MITRAL CONTOUR SYSTEM (CARDIAC DIMENSIONS, KIRKLAND, WA, USA)

The Carillon device is an indirect annuloplasty device delivered by the transjugular approach. It consists of two self-expanding nitinol anchors connected by a nitinol curvilinear segment (different lengths are available), which are implanted in the coronary sinus, in close proximity to the posterior annulus of the MV. Carillon obtained CE mark in 2011. The TITAN trial evaluated the clinical impact of the Carillon in heart failure subjects with significant FMR and showed a significant reduction in FMR grade (effective regurgitant orifice area [EROA] 0.23 ± 0.07 cm² to 0.12 ± 0.08 cm² and regurgitant volume 34 ± 10 ml to 17 ± 12 ml) at one-year follow-up⁴⁰.

Treated subjects were compared with a pseudo-control group consisting of subjects without implants. Functional and performance status significantly improved in the treated subjects⁴¹. The REDUCE FMR trial, a blinded, randomised (3:1) sham-controlled trial in about 180 patients, has completed enrolment in Europe, Australia and New Zealand and will probably be reported before the end of 2018. A pivotal trial in the USA in which patients with secondary MR will be randomised 2:1 to receive the device versus optimal medical therapy is soon to be underway.

Some anatomical limitations explain why this approach cannot be effective in a relevant proportion of patients with FMR.

First of all, the coronary sinus and mitral annulus are not coplanar. Moreover, depending on the individual coronary anatomy, there is a risk of coronary artery compression that may preclude patient eligibility. The main advantages are that the procedure is technically easy to perform, can be carried out under local anaesthesia and in centres without on-site cardiac surgery, and is safe.

ARTO™ SYSTEM (MVRX, INC., SAN MATEO, CA, USA)

The ARTO is an indirect annuloplasty device that consists of a suture connecting two anchors, one implanted in the interatrial septum and one in the coronary sinus. The tensioning of the connecting suture shortens the anteroposterior diameter of the mitral annulus, resulting in a reduction of the anteroposterior mitral annular diameter and improved leaflet coaptation.

In the early feasibility MAVERIC trial, 11 high-risk patients with FMR grade $\geq 2+$ underwent successful ARTO System implantation, with no procedural safety events. Six-month follow-up showed improvements in MR grade (about 80% of the patients with MR ≤ 2 , PISA from 30.3 ± 11.1 mm² to 13.7 ± 8.6 mm²), as well as in functional status⁴². Phase II trial enrolment is ongoing.

The main concern regarding indirect annuloplasty is the total lack of surgical background.

DIRECT ANNULOPLASTY

CARDIOBAND™ (EDWARDS LIFESCIENCES)

The Cardioband is the transcatheter device closest to a surgical ring and is the direct annuloplasty system with the widest clinical experience so far, having been implanted in about 500 patients with FMR. It is delivered from a fully percutaneous transeptal approach and the implant is performed on the atrial side of the mitral annulus. An incomplete adjustable surgical-like Dacron band is implanted from the lateral to the medial trigone, under live echo and fluoroscopic guidance, using multiple retrievable 6 mm anchor elements. The size of the band is determined by preoperative angio-CT assessment, which is performed also to rule out the presence of annular calcifications (the main anatomical contraindication to this procedure) and the proximity of the circumflex coronary artery. After implantation, the Cardioband length may be shortened on the beating heart under live echo guidance to reduce the antero-septal diameter of the mitral annulus, improve leaflet coaptation and reduce MR.

The Cardioband obtained CE mark approval at the end of 2014. Results from the early feasibility trial (30 high-risk patients with significant FMR) showed a procedural success rate of 100%, with no periprocedural deaths and a 30-day mortality of 5%. Adjustment of the implanted Cardioband reduced the annular septolateral dimension by $>30\%$ (from 3.7 ± 0.5 cm at baseline to 2.5 ± 0.4 cm after one month and to 2.4 ± 0.4 cm after six months). Residual MR was $\leq 2+$ in 86.3% of patients at six-month follow-up. Significant improvement in NYHA class, functional status and quality of life was also reported^{43,44}. Limited late follow-up suggests that MR reductions may be durable. The partial design of the band may represent an issue in terms of long-term durability, since usually in surgery complete prosthetic rings are used in the

context of FMR. However, the reduction in septolateral dimension of about 30% observed in the trial is absolutely comparable with the one obtained in surgery after undersized annuloplasty with complete rings.

IRIS TRANSCATHETER ANNULOPLASTY RING (MILLIPEDE MEDICAL, SANTA ROSA, CA, USA)

The IRIS annuloplasty system is a semi-rigid complete adjustable ring with a nitinol frame, which is placed on the atrial surface of the mitral annulus, via the transeptal approach, by means of multiple anchor elements. Successful first-in-human transeptal implantation was announced in May 2017⁴⁵.

AMEND™ (VALCARE MEDICAL, HERZLYIA PITUACH, ISRAEL)

The AMEND is a complete, semi-rigid, D-shaped mitral ring, which is implanted on the atrial side of the mitral annulus by means of 12 anchors, through the transapical access. Successful first-in-man implantation has recently been reported, and a fully percutaneous transeptal device is under preclinical evaluation⁴⁶.

Being a complete annuloplasty device, it can potentially serve as a platform for future valve-in-ring implantation.

MITRAL RESTRICTION RING (CARDIAC IMPLANT SOLUTIONS LLC, JACKSONVILLE, FL, USA)

The Mitral Restriction Ring is another direct annuloplasty device delivered via the transeptal route, which is currently under pre-clinical investigation. It allows the implantation of a complete adjustable mitral ring with an internal cinching wire on the atrial annular side by means of multiple anchor elements. The implantable actuator is designed to enable non-invasive chronic progressive cinching at follow-up, following the completion of tissue healing (KH Kuck. Cardiac Implants Direct Annuloplasty for Functional MR: Device, Procedure, and Outcomes. TCT 2017, Denver, CO, USA. Available at <https://www.tctmd.com/slide/cardiac-implants-direct-annuloplasty-functional-mr-device-procedure-and-outcomes>).

LV REMODELLING DEVICES

To address ventricular abnormalities as the underlying cause of MR, the VenTouch system and the AccuCinch have been developed as ventricular reshaping devices.

The VenTouch™ system (Mardil Medical, Minneapolis, MN, USA), which was first implanted in humans in 2014, consists of a bladder that is positioned over the posterior-septal lateral aspects of the LV using a left thoracotomy, and inflated to reduce the dimensions of the LV and the mitral annulus, improving leaflet coaptation^{12,47}.

The AccuCinch® (Ancora Heart, Santa Clara, CA, USA) is a device consisting of a series of nitinol anchors that are deployed subvalvular on the ventricular side of the mitral annulus, using a transfemoral, retro-aortic approach. A tension cable enables adjustment and consequent ventriculoplasty on the heart, resulting in MR reduction. The AccuCinch is currently under investigation in early feasibility human studies⁴⁸.

The proof of concept for ventricular reshaping was suggested by the randomised RESTOR-MV trial, in which a tether implanted

through the LV cavity resulted in chamber remodelling and decreased MR, with a positive impact on patient survival⁴⁹.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

At the moment, the decision between the different approaches is mainly based on operator experience, anatomic exclusions for the different devices, and availability of the different technologies, since comparative evidence to support one specific device or category over another in the different clinical settings simply does not exist.

If we assume that transcatheter mitral interventions are the natural evolution of modern mitral valve surgery, the indications may continue to move from a palliative target (improving symptoms, treating advanced and end-stage disease) towards the aim of improving prognosis by an early indication. Early results show a high safety profile for these procedures, but effectiveness requires further study.

Improvement of advanced imaging for patient screening and procedural guidance will play a fundamental role in patient selection and optimisation of the outcomes. Another key point is the specific training of structural mitral operators, that should ideally include a common educational pathway with interventional, surgical and imaging knowledge.

Finally, it will be of extreme importance to collect proper evidence in a rigorous way, in order to support the different decisions in the different clinical scenarios. It is likely that transcatheter mitral repair will explode as TAVI did before, but this will take more time due to a greater clinical and technical complexity, keeping in mind that both the patient and the physician are always in the middle of this technological “revolution”⁵⁰.

Conclusions

Several categories of device are currently available for transcatheter mitral valve repair. They are at different phases of clinical evaluation in a field which is expanding extremely rapidly. Transcatheter mitral valve replacement is quickly becoming clinically available, expanding the available portfolio, in the absence of clear indications or recommendations, for specific patient subsets.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
2. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med*. 1996;335:1417-23.
3. Anyanwu AC, Adams DH. Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. *Semin Thorac Cardiovasc Surg*. 2007;19:90-6.
4. Crabtree TD, Bailey MS, Moon MR, Munfakh N, Pasque MK, Lawton JS, Moazami N, Aubuchon KA, Al-Dadah AS, Damiano RJ

Jr. Recurrent mitral regurgitation and risk factors for early and late mortality after mitral valve repair for functional ischemic mitral regurgitation. *Ann Thorac Surg.* 2008;85:1537-42.

5. Taramasso M, Maisano F. Valvular disease: Functional mitral regurgitation: should all valves be replaced? *Nat Rev Cardiol.* 2016;13:65-6.

6. Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. *J Thorac Cardiovasc Surg.* 2012;144:308-12.

7. Detaint D, Sundt TM, Nkomo VT, Scott CG, Tajik AJ, Schaff HV, Enriquez-Sarano M. Surgical correction of mitral regurgitation in the elderly: outcomes and recent improvements. *Circulation.* 2006;114:265-72.

8. AATS Ischemic Mitral Regurgitation Consensus Guidelines Writing Committee, Kron IL, LaPar DJ, Acker MA, Adams DH, Ailawadi G, Bolling SF, Hung JW, Lim DS, Mack MJ, O'Gara PT, Parides MK, Puskas JD. 2016 update to The American Association for Thoracic Surgery (AATS) consensus guidelines: Ischemic mitral valve regurgitation. *J Thorac Cardiovasc Surg.* 2017;153:e97-114.

9. Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg.* 2005;27:847-53.

10. De Bonis M, Taramasso M, Grimaldi A, Maisano F, Calabrese MC, Verzini A, Ferrara D, Alfieri O. The GeoForm annuloplasty ring for the surgical treatment of functional mitral regurgitation in advanced dilated cardiomyopathy. *Eur J Cardiothorac Surg.* 2011;40:488-95.

11. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J.* 2007;28:1358-65.

12. Sorajja P, Maisano F. Percutaneous Treatment for Native Mitral Regurgitation. *Prog Cardiovasc Dis.* 2017;60:405-14.

13. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, Hung JW, Voisine P, Dagenais F, Gillinov AM, Thourani V, Argenziano M, Gammie JS, Mack M, Demers P, Atluri P, Rose EA, O'Sullivan K, Williams DL, Bagiella E, Michler RE, Weisel RD, Miller MA, Geller NL, Taddei-Peters WC, Smith PK, Moquete E, Overbey JR, Kron IL, O'Gara PT, Acker MA; CTSN. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. *N Engl J Med.* 2016;374:344-53.

14. Petronio AS, Capranzano P, Barbato E, Piazza N, Baumbach A, Haude M, Windecker S. Current status of transcatheter mitral valve therapy in Europe: results from an EAPCI survey (Part II). *EuroIntervention.* 2017;12:1934-9.

15. Taramasso M, Pozzoli A, Basso C, Thiene G, Denti P, Kuwata S, Nietlispach F, Alfieri O, Hahn RT, Nickenig G, Schofer J,

Leon MB, Reisman M, Maisano F. Compare and contrast tricuspid and mitral valve anatomy: interventional perspectives for transcatheter tricuspid valve therapies. *EuroIntervention.* 2018;13:1889-98.

16. Maisano F, Alfieri O, Banai S, Buchbinder M, Colombo A, Falk V, Feldman T, Franzen O, Herrmann H, Kar S, Kuck KH, Lutter G, Mack M, Nickenig G, Piazza N, Reisman M, Ruiz CE, Schofer J, Sondergaard L, Stone GW, Taramasso M, Thomas M, Vahanian A, Webb J, Windecker S, Leon MB. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? *Eur Heart J.* 2015;36:1651-9.

17. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walthert T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739-91.

18. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70:252-89.

19. Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A, Kar S, Thourani V, Ailawadi G. Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report. *J Am Coll Cardiol.* 2017;70:2315-27.

20. Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, Whitlow PL, Rinaldi MJ, Grayburn P, Mack MJ, Mauri L, McCarthy PM, Feldman T. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol.* 2014;64:172-81.

21. Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol.* 2013;62:1052-61.

22. Kalbacher D, Schäfer U, von Bardeleben RS, Zuern CS, Bekerdedjian R, Ouarrak T, Sievert H, Nickenig G, Boekstegers P, Senges J, Schillinger W, Lubos E. Impact of tricuspid valve regurgitation in surgical high-risk patients undergoing MitraClip implantation: results from the TRAMI registry. *EuroIntervention.* 2017;12:e1809-16.

23. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekerdedjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J.* 2016;37:703-12.

24. Taramasso M, Maisano F, Latib A, Denti P, Buzzatti N, Cioni M, La Canna G, Colombo A, Alfieri O. Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation. *EuroIntervention*. 2014;10:746-52.
25. Grasso C, Buccheri S, Capodanno D, Popolo Rubbio A, Di Salvo ME, Scandura S, Mangiafico S, Salerno T, Cannata S, Dezio V, Castania G, Barbanti M, Capranzano P, Tamburino C. Strategies and Outcomes of Repeat Mitral Valve Interventions after Failed MitraClip Therapy. *Cardiology*. 2017;137:114-20.
26. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, Hermiller JB, Heimansohn D, Gray WA, Grayburn PA, Mack MJ, Lim DS, Ailawadi G, Herrmann HC, Acker MA, Silvestry FE, Foster E, Wang A, Glower DD, Mauri L; EVEREST II Investigators. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844-54.
27. Tigges E, Blankenberg S, von Bardeleben RS, Zurn C, Bekeredjian R, Ouarrak T, Sievert H, Nickenig G, Boekstegers P, Senges J, Schillinger W, Lubos E. Implication of pulmonary hypertension in patients undergoing MitraClip therapy: results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail*. 2018;20:585-94.
28. Geis NA, Puls M, Lubos E, Zuern CS, Franke J, Schueler R, von Bardeleben RS, Boekstegers P, Ouarrak T, Zahn R, Ince H, Senges J, Katus HA, Bekeredjian R. Safety and efficacy of MitraClip™ therapy in patients with severely impaired left ventricular ejection fraction: results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail*. 2018;20:598-608.
29. Armeni P, Boscolo PR, Tarricone R, Capodanno D, Maggioni AP, Grasso C, Tamburino C, Maisano F. Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation. *Int J Cardiol*. 2016;209:153-60.
30. Guerin P, Bourguignon S, Jamet N, Marque S. MitraClip therapy in mitral regurgitation: a Markov model for the cost-effectiveness of a new therapeutic option. *J Med Econ*. 2016;19:696-701.
31. Tamburino C, Buccheri S, Popolo Rubbio A, Scandura S, Di Salvo ME, Mangiafico S, Immé S, Caruso G, Scalia M, Condorelli A, Barbanti M, Capranzano P, Capodanno D, Grasso C. Feasibility and predictors of early discharge after percutaneous edge-to-edge mitral valve repair. *Heart*. 2017;103:931-6.
32. Praz F, Spargias K, Chrissoheris M, Büllsfeld L, Nickenig G, Deuschl F, Schueler R, Fam NP, Moss R, Makar M, Boone R, Edwards J, Moschovitis A, Kar S, Webb J, Schafer U, Feldman T, Windecker S. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. *Lancet*. 2017;390:773-80.
33. von Bardeleben RS, Colli A, Schulz E, Ruf T, Wrobel K, Vahl CF, Gerosa G, Werner C, Münzel T, Beiras-Fernandez A. First in human transcatheter COMBO mitral valve repair with direct ring annuloplasty and neochord leaflet implantation to treat degenerative mitral regurgitation: feasibility of the simultaneous toolbox concept guided by 3D echo and computed tomography fusion imaging. *Eur Heart J*. 2018;39:1314-5.
34. Seeburger J, Rinaldi M, Nielsen SL, Salizzoni S, Lange R, Schoenburg M, Alfieri O, Borger MA, Mohr FW, Aidiatis A. Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT Trial (Transapical Artificial Chordae Tendinae) proof of concept. *J Am Coll Cardiol*. 2014;63:914-9.
35. Colli A, Bagozzi L, Banchelli F, Besola L, Bizzotto E, Pradegan N, Fiocco A, Manzan E, Zucchetta F, Bellu R, Pittarello D, Gerosa G. Learning curve analysis of transapical NeoChord mitral valve repair. *Eur J Cardiothorac Surg*. 2018;54:273-80.
36. Colli A, Manzan E, Aidiatis A, Rucinskas K, Bizzotto E, Besola L, Pradegan N, Pittarello D, Janauskas V, Zakarkaite D, Drasutiene A, Lipnevicius A, Danner BC, Sievert H, Vaskelyte L, Schnelle N, Salizzoni S, Marro M, Rinaldi M, Kurnicka K, Wrobel K, Ceffarelli M, Savini C, Pacini D, Gerosa G. An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. *Eur J Cardiothorac Surg*. 2018 Mar 5. [Epub ahead of print].
37. Gammie JS, Bartus K, Gackowski A, D'Ambra MN, Szymanski P, Bilewska A, Kusmierczyk M, Kapelak B, Ruzicidlo-Resil J, Moat N, Duncan A, Yadev R, Livesey S, Diprose P, Gerosa G, D'Onofrio A, Pitterello D, Denti P, La Canna G, De Bonis M, Alfieri O, Hung J, Kolsut P. Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal Implantation Device: A Prospective Trial. *J Am Coll Cardiol*. 2018;71:25-36.
38. Badhwar V, Bolling SF. Mitral valve surgery in the patient with left ventricular dysfunction. *Semin Thorac Cardiovasc Surg*. 2002;14:133-6.
39. Taramasso M, Maisano F. Transcatheter mitral valve repair-transcatheter mitral valve annuloplasty. *EuroIntervention*. 2014;10 Suppl U:U129-35.
40. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, Fajadet J, Shah AM, Feldman T, Kaye DM, Goldberg SL, Levy WC, Solomon SD, Reuter DG. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. *Eur J Heart Fail*. 2012;14:931-8.
41. Lipiecki J, Siminiak T, Sievert H, Müller-Ehmsen J, Degen H, Wu JC, Schandrin C, Kalmucki P, Hofmann I, Reuter D, Goldberg SL, Haude M. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. *Open Heart*. 2016;3:e000411.
42. Rogers JH, Thomas M, Morice MC, Narbute I, Zabunova M, Hovasse T, Poupineau M, Rudzitis A, Kamzola G, Zvaigzne L, Greene S, Erglis A. Treatment of Heart Failure With Associated Functional Mitral Regurgitation Using the ARTO System: Initial Results of the First-in-Human MAVERIC Trial (Mitral Valve Repair Clinical Trial). *JACC Cardiovasc Interv*. 2015;8:1095-104.
43. Maisano F, Taramasso M, Nickenig G, Hammerstingl C, Vahanian A, Messika-Zeitoun D, Baldus S, Huntgeburth M,

- Alfieri O, Colombo A, La Canna G, Agricola E, Zuber M, Tanner FC, Topilsky Y, Kreidel F, Kuck KH. Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial. *Eur Heart J*. 2016;37:817-25.
44. Nickenig G, Hammerstingl C, Schueler R, Topilsky Y, Grayburn PA, Vahanian A, Messika-Zeitoun D, Urena Alcazar M, Baldus S, Volker R, Huntgeburth M, Alfieri O, Latib A, La Canna G, Agricola E, Colombo A, Kuck KH, Kreidel F, Frerker C, Tanner FC, Ben-Yehuda O, Maisano F. Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation: 6-Month Results With the Cardioband Percutaneous Mitral Repair System. *JACC Cardiovasc Interv*. 2016;9:2039-47.
45. Rogers JH, Boyd WD, Smith TWR, Ebner AA, Bolling SF. Combined MitraClip Edge-to-Edge Repair With Millipede IRIS Mitral Annuloplasty. *JACC Cardiovasc Interv*. 2018;11:323-4.
46. Gerosa G, Besola L, Manzan E, Bizzotto E, Zucchetta F, Pittarello D, Tarantini G, Meerkink D, Colli A. First-in-Human of Catheter-Delivered Annuloplasty Ring to Treat Functional Mitral Regurgitation. *JACC Cardiovasc Interv*. 2016;9:e211-3.
47. Sorajja P, Leon MB, Adams DH, Webb JG, Farivar RS. Transcatheter Therapy for Mitral Regurgitation Clinical Challenges and Potential Solutions. *Circulation*. 2017;136:404-17.
48. Gooley RP, Meredith IT. The Accucinch transcatheter direct mitral valve annuloplasty system. *EuroIntervention*. 2015;11 Suppl W:W60-1.
49. Grossi EA, Patel N, Woo YJ, Goldberg JD, Schwartz CF, Subramanian V, Feldman T, Bourge R, Baumgartner N, Genco C, Goldman S, Zenati M, Wolfe JA, Mishra YK, Trehan N, Mittal S, Shang S, Mortier TJ, Schweich CJ Jr; RESTOR-MV Study Group. Outcomes of the RESTOR-MV Trial (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). *J Am Coll Cardiol*. 2010;56:1984-93.
50. Capodanno D. Transcatheter aortic valve implantation and mitral valve repair: two trains, two speeds. *EuroIntervention*. 2017;12:1921-4.