TRANSCATHETER OPTIONS FOR TREATMENT OF MITRAL REGURGITATION

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Disclosure: No potential conflict of interest.
Received: 21.11.14 **Accepted:** 08.01.15
Citation: EMJ Cardiol. 2015;3[1]:48-56.

ABSTRACT

Transcatheter therapy for valvular heart disease (VHD) as an alternative for surgery, as the standard of care, has emerged rapidly over the last 10 years. Since the first transcatheter heart valve (THV) implantation in pulmonary position, in 2000, and in aortic position, in 2002, an enormous number of high-risk patients have undergone percutaneous aortic valve implantation and a wide variety of commercially available THVs have emerged within the medical sector. Interventional mitral valve repair (MVR) and implantation started with a variety of devices developed by industry, but few are available at the moment. In this article percutaneous systems for the treatment of mitral regurgitation (MR) in high-risk patients are introduced and discussed. Technologies currently under development can be classified by their anatomical approach. To date, only the percutaneous edge-to-edge approach is applied on a larger scale in clinical routine with the MitraClip device. Several other technologies for percutaneous MVR have achieved first-in-man results. For comparable results of transcatheter MVR to surgical MVR a combination of these technologies may be required. The field of transcatheter mitral valve implantation is evolving quickly as well. With half a dozen devices under development right now and a few entering the clinical test stage it may be just a matter of time until a THV for the mitral position will become commercially available. Considering that MR is among the most frequent entities in VHD and, furthermore, that life expectancy will continue to increase, it can be anticipated that in the near future there will be percutaneous strategies needed for the treatment of MR in high-risk patients. At present, all devices have to be restricted to inoperable patients or to compassionate use settings. However, once clinical proof of safety and efficacy have been demonstrated, extension to a broader patient spectrum seems likely. To ensure cautious and safe clinical introduction of these novel therapeutic options, guidance by interdisciplinary dedicated heart teams is of paramount importance.

Keywords: Mitral regurgitation, mitral valve repair, minimally-invasive, transcatheter mitral valve repair, MitraClip, heart team.

INTRODUCTION

Transcatheter therapy for valvular heart disease (VHD) as an alternative for surgery, as the standard of care, has emerged rapidly over the last 10 years.[1] Since the first transcatheter heart valve (THV) implantation in pulmonary position in 2000, and in aortic position in 2002, an enormous number of high-risk patients have undergone percutaneous aortic valve implantation and a wide variety of commercially available THV have penetrated the medical sector.[2,3] Transcatheter mitral valve repair (TMVR) and mitral valve implantation (TMVI) started with a variety of devices developed by the industry, but only a few are available at the moment. Currently there is only one catheter-based leaflet repair system with published randomised trial data available: the MitraClip (Abbott Laboratories, Abbott Park, IL, USA), which mimics the surgical edge-to-edge MVR initially described by Alfieri and co-workers.[4,5] Despite that, a great number of alternative technologies are under development right now. These systems can be classified by the point of application, following established surgical approaches for MVR and MVI.[6] Considering that mitral regurgitation (MR) is among the most frequent entities in VHD, with a prevalence of 1.7% in Western societies, and furthermore life expectancy will continue to increase, it can be anticipated that, in the near future, there will be percutaneous strategies needed for the treatment of MR in high-risk patients.[7-9] In low-risk patients it has to be emphasised that all novel percutaneous and endovascular strategies for MVR and MVI have to compete with mitral valve (MV) surgery, which is the gold standard of MR treatment, and shows low perioperative risk and excellent long-term outcome.[10] In high-risk patients effectivity can not be compared to surgical outcomes due to a large proportion of patients who are denied surgery.

TRANSCATHETER OPTIONS FOR MVR AND MVI

Even though surgical intervention is recommended in patients with symptomatic severe MR or asysmptomatic severe MR with left ventricular (LV) dysfunction or enlargement, only 50% of these patients receive surgical treatment.[11,12] This is mainly due to advanced age, relevant comorbidities, and/or impaired LV function of the other 50% and thus, denial of surgery. In the following, percutaneous systems for treatment of MR in high-risk patients are introduced.

The Leaflet Approach

Leaflet plication

The aim of the leaflet plication technique is to create a 'double orifice' by bringing the anterior mitral leaflet (AML) and posterior mitral leaflet (PML) together, as first described by Alfieri et al.[5] as surgical procedure. The surgeon places a suture between the A2 and P2 segment of the mitral leaflets. Thereby leaflet coaptation is re-established and MR is minimised. Advantages of the edge-to-edge technique are the simplicity and the possibility of customisation on the basis of the location of the regurgitant jet with both central and paracommissural leaflet approximation. The edge-to-edge technique always involves the risk of creating a mitral valve stenosis. Transcatheter techniques follow this approach with different access routes.

The MitraClip system (Figure 1A and 1B) consists of a polyester-covered cobalt-chromium clip. It is introduced by a 24 Fr delivery catheter via the femoral vein into the right atrium (RA) and, after transseptal puncture, advanced into the left atrium (LA). Under 2D and 3D echocardiographic and fluoroscopic guidance, the clip is positioned above the MV, opened, and advanced into the LV. Subsequently, it is retracted so that the free edges of AML and PML are loaded onto the clip at the origin of the regurgitant jet; closure of the clip results in a 'double-orifice' MV. The MitraClip system was initially evaluated in the EVEREST I (Endovascular Valve Edge-to-Edge Repair Study) and EVEREST II trials.[13,14] Out of 107 patients, acute success with residual MR ≤Grade 2+ was noted in 74%. In 66% of successfully implanted patients, MR was ≤Grade 2+ at 12 months. Severe adverse events were documented in 9% at 30 days. Randomisation for the EVEREST II trial[15] allocated 279 patients in a 2:1 ratio to MitraClip or surgery. Degenerative MR was present in 73% of patients. Primary efficacy endpoint was defined as survival, freedom from reoperation, and freedom from MR ≥Grade 2+ at 12 months, and it was reached in 55% of interventional and 73% of surgical patients in an intent-to-treat analysis ($p=0.007$). The combined safety endpoint (incidence of severe adverse events to 30 days) was reached in 15% of interventional and 48% of surgical patients ($p<0.001$), even though transfusion of ≥2 units represented the majority of adverse events. Excluding transfusion, no significant difference in safety was seen ($p=0.23$). In both interventional and surgical cohorts, ventricular remodelling, improved New York Heart Association (NYHA) functional class, and improved quality of life were noted. It has to be emphasised that 20% of MitraClip patients underwent secondary MV surgery. In 46% of interventional patients MR was ≥Grade 2+ at 12 months. Further follow-up resulted in MitraClip FDA approval in October 2013. Efficacy of the MitraClip device is currently evaluated in randomised controlled trials against best medical therapy in the COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy)[16] and RESHAPE-HF (MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation)[17] trials.

Extensive real-world experience with the MitraClip system exists in Europe. The first implantation performed in Europe was at the University Heart Center in Hamburg, Germany, in January 2008. In an interim analysis of 51 patients,[18] marked reduction of MR and an excellent safety profile of the procedure was documented. Until January 2014, >500 patients have been treated. This represents the world´s largest single-centre experience. Meanwhile 2-year data of 202 successfully treated patients (74±9 years, 65% male, The logistic European System for Cardiac Operative Risk Evaluation I 25 [16-43]%) from our centre have been reported.[19] 140 patients were treated for secondary MR, while primary MR was present in 62 patients. Freedom from MR ≥Grade 2+ was 89% at 2 years. Presently, a second device for leaflet plication is undergoing preclinical testing: the Mitraflex system (TransCardiac Therapeutics, Atlanta, GA, USA) combines the possibility of deploying a clip for leaflet plication and implanting an artificial chord during the same procedure via the transapical route.

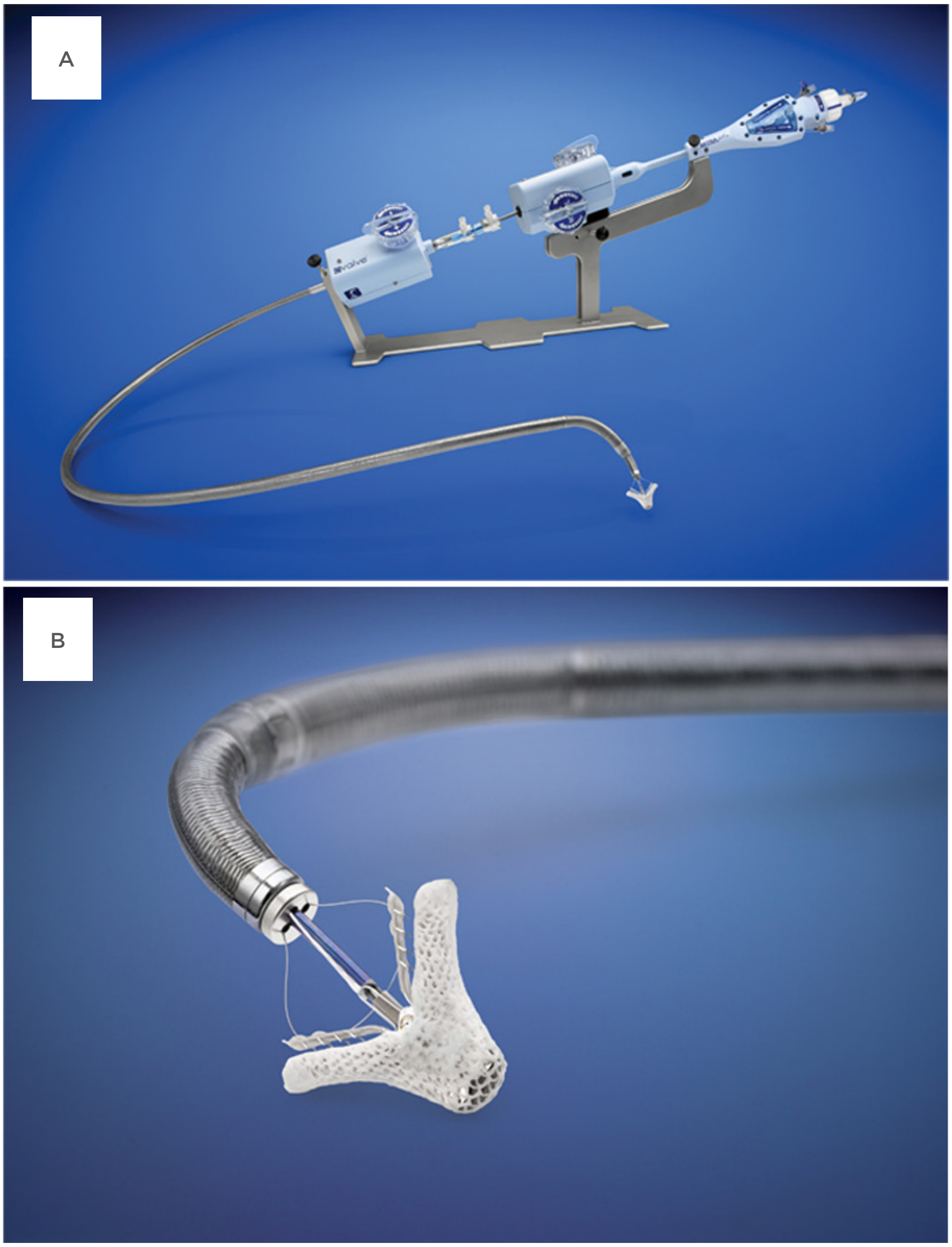

Figure 1: The MitraClip system consists of a polyester-covered cobalt-chromium clip. It represents the interventional extension of the surgical 'edge-to-edge' technique. Displayed here are the delivery system (A) and the clip (B).

Reproduced from Abbott Vascular®, Menlo Park, CA, USA

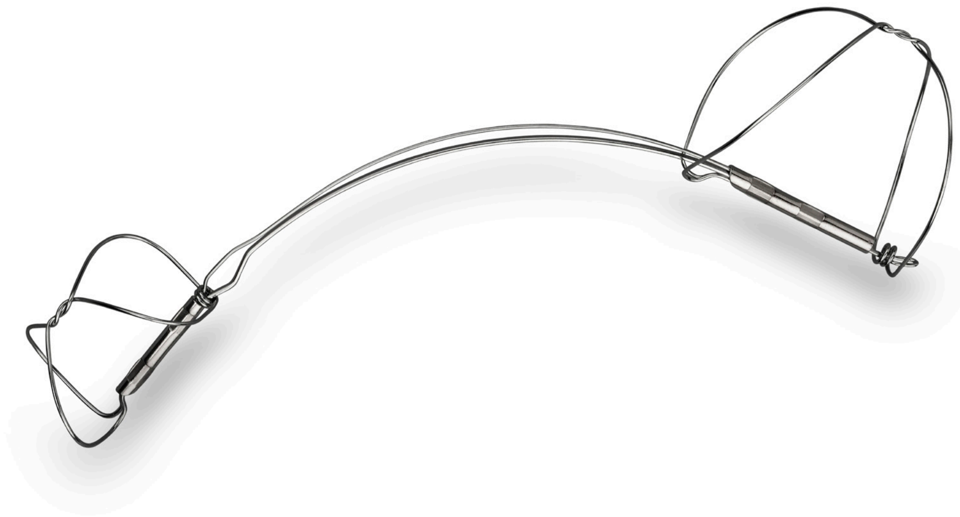

Figure 2: The Carillon Mitral Contour System consists of a central nitinol element connecting distal anchors and a proximal anchor.
Reproduced from Cardiac Dimensions®, Inc., Kirkland, WA, USA

Leaflet ablation

For treatment of degenerative MR the leaflet ablation technique can be used. The Thermocool irrigation ablation electrode (Biosense Webster, Inc., Diamond Bar, CA, USA) applies radiofrequency energy to the leaflets, thus reducing motion by inducing fibrosis. Feasibility was proven in the animal model.[20]

Leaflet coaptation

The principle of space occupying in the regurgitant orifice is implemented by the Mitra Spacer™ device (Cardiosolutions, Stoughton, MA, USA), which is currently undergoing Phase I trial. A balloon-shaped spacer, percutaneously transseptal delivered and made of a polyurethane-silicone polymer, is advanced into the mitral orifice and anchored to the LV apex. The device acts like a buoy and provides a surface the leaflets can coapt against, thus reducing MR.[21]

The Annuloplasty Approach

Indirect annuloplasty

The anatomical proximity of the coronary sinus (CS) to the posterior aspect of the mitral annulus (MA) and the uncomplicated transvenous access have led to the development of different systems for indirect annuloplasty. The Carillon Mitral Contour System (Cardiac Dimensions®, Inc., Kirkland, WA, USA) (Figure 2) consists of a central nitinol element connecting distal anchors and a proximal anchor. After transjugular access the anchoring portions are placed in the vena cordis magna and proximal CS. By stepwise foreshortening of the central element, the device allows for remodelling of the posterior periannular tissue. Results of the prospective, multicentre AMADEUS trial (Carillon Mitral Annuloplasty Device European Union Study)[22] have been published. Implantation of the device was successful in 30 of 48 patients (63%). The device carries a Conformité Européenne (CE) mark. The Monarc System (Edwards Lifesciences, Irvine, CA, USA) has self-expanding distal and proximal anchoring segments connected by a central spring. This spring is held under tension by resorbable spacers. During the first weeks following implantation, the central portion foreshortens successively and reduces septal-lateral circumference of the MA. 1-year data of the multicentre EVOLUTION-I trial[23] (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for The

Treatment of Mitral Regurgitation) have been published. In 82% of 72 patients, successful implantation was documented. In 30%, compression of coronary arteries was noted. The primary safety endpoint was reached by 91% and 82% at 30 days and 12 months, respectively. In 50%, reduction of MR by ≥1 Grade was noted at 12 months. In light of these results, the device is no longer available.

Currently, devices are under development which add a second traction force on the LA or RA. A device by St. Jude Medical (Minneapolis, MN, USA) implants helical screws into the myocardium at the posteromedial mitral annulus. Feasibility was proven in pigs.[24] The National Institutes of Health cerclage technology also proved feasibility in the animal model of a suture and tension-fixation device.[25] It has to be emphasised that with increasing diameter of the atrium, the distance of the CS to the mitral plane is also increasing, mainly in the posterolateral location. Thus, it can be anticipated that the indirect annuloplasty approach should be considered suitable for small atriums in short-term MR.[26-28]

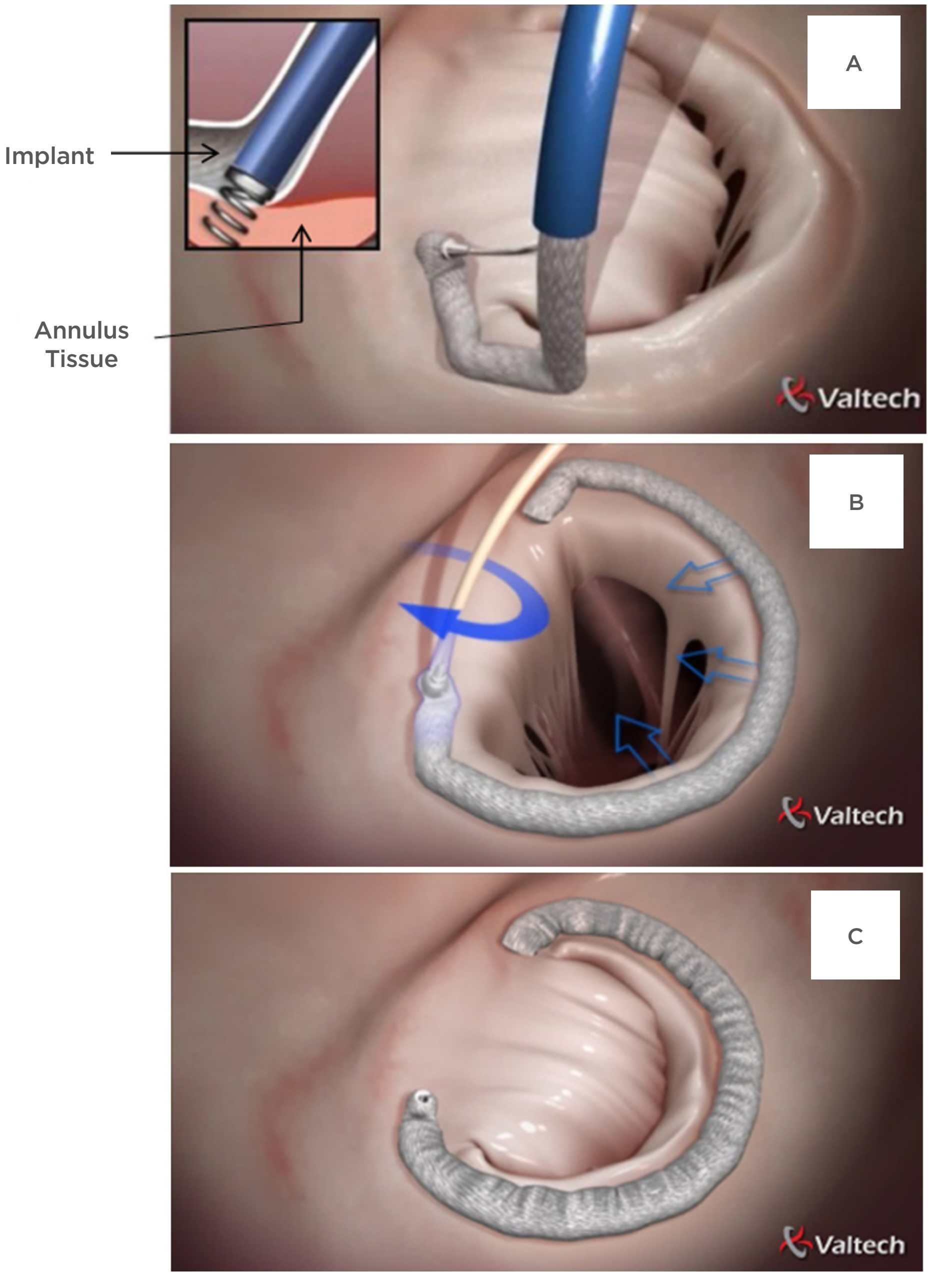

Figure 3: The Valtech Cardio B uses nitinol screws inserted into the atrial aspect of the mitral annulus (A). Subsequently the annulus is cinched (B) until mitral regurgitation decreases (C).
Reproduced from Valtech Cardio®, Or Yehuda, Israel

Direct annuloplasty

Several devices for direct annuloplasty exist mimicking surgical annuloplasty. The risk of circumflex artery compression inherent with CS approaches is reduced by these techniques. One of the devices with early clinical experience is the Valtech Cardio B (Valtech Cardio, Or Yehuda, Israel) (Figure 3A-C), which is delivered via a transvenous, transseptal route, and uses nitinol screws inserted into the atrial aspect of the MA in a commissure-to-commissure fashion. In a second step, a wire is tightened to allow for cinching of the annulus. Experimental and early clinical data have been presented.[29] The Mitralign system (Mitralign Inc., Tewksbury, MA, USA) delivers pledgets via a transventricular route and after puncture of the MA to the atrial aspect. Pledgets are cinched by a suture. A CE mark study is currently being persued.[30] The Quantum Cor device (QuantumCor, Lake Forest, CA, USA) has been tested in animal models and works with heat energy applied to the MA, causing constriction.[31] Hybrid solutions, with surgical implantation of an annuloplasty ring and postoperative adjustment of that ring via transseptal access, are currently under pre-clinical development: the Dynamic annuloplasty Ring System (MiCardia, Inc., Irving, CA, USA) and the Adjustable Annuloplasty Ring (MitralSolutions, Fort Lauderdale, FL, USA).

The Chordal Approach

A novel device for transapical implantation of neochordae has been evaluated clinically, and recently received a CE mark (NeoChord DS1000, NeoChord Inc., Minneapolis, MN, USA). Via standard transapical access, the delivery catheter is inserted into the LV. Under 2D and 3D echocardiographic guidance, the free edge of the prolapsing segment of PML or AML are grasped. Colour-sensitive fibre optics ensure grasping of sufficient leaflet tissue. Neochordae are subsequently externalised through the LV apex and fixed at adequate length under echo guidance. Clinical feasibility and safety have recently been demonstrated in the Transapical Artificial Chordae Tendineae trial and further evaluation is being pursued in a post-market registry at present.[32]

The LV Remodelling Approach

In patients with ischaemic or cardiomyopathy-induced functional MR, a reduction of LV dimensions can lead to a reduction of MR. The idea is to decrease the septal-lateral annular distance and bring the LV papillary muscles to the leaflets by reducing the anterior-posterior dimension of the LV. Currently there is one device following this principle: the Mardil-BACE (Mardil, Inc., Morrisville, NC, USA) has shown feasibility in the animal model and proof-of-concept demonstration in 15 patients. The device is implanted into a beating heart through a mini-thoracotomy with placement of a silicone band around the atrioventricular groove. Inflatable chambers are built in the silicone band and can be inflated at the height of the MA. After implantation adjustment is possible for better leaflet coaptation.

Transcatheter mitral valve implantation (TMVI)

Recently, very early clinical experience has been gathered with devices for transapical and transatrial TMVI. These new devices have the conceptual advantages of potentially abolishing MR altogether without risk of recurrence. Contrary to the aortic valve the anatomy of the MV leads to a challenging development process regarding paravalvular leakage and left ventricular outflow tract (LVOT) obstruction. The eccentric geometry of the mitral orifice does not allow simple solutions for device delivery and anchoring. Nitinol-based devices, which are currently under development, are the Endovalve (Micro Interventional Devices, Inc., Newtown, PA, USA) device, the former Lutter-Lozonschi, now Tendyne valve (Tendyne Holdings, Roseville, MI, USA), the CardiAQ (CardiAQ valve Technologies Inc, Irvine, CA, USA) device, the Edwards Fortis (Edwards Lifesciences, Irvine, CA, USA), the MitrAssist (MitrAssist Ltd., Misgav, Israel) device, and the NeoVasc Tiara (NeoVasc Inc., Richmond, Canada).

The Endovalve is implanted via a right mini-thoracotomy and delivery of the catheter-based valve through the LA. The prosthesis consists of a ring and leaflets with a foldable tripod frame. A gripper feature is integrated for attachment in the beating heart. While a true percutaneous version is under development, the thoracotomy approach was successfully tested in the animal model. The Lutter-Lozonschi, now Tendyne valve, is also radially self-expandable and is delivered via a transapical approach. It consists of an atrial fixation system, a tubular piece with a mounted tricuspid pericardial valve, and a ventricular fixation system. First-in-men procedures were undertaken in Paraguay with promising results.

It has to be emphasised that both patients received a conventional MVR 2 hours after TMVI.[33] First-in-men experiences were made with the Edwards Fortis valve in London, UK and Bern, Switzerland.[34] The valve consists of a central valve body, paddles, and an atrial flange and is only available in 29 mm. The valve is nitinol-based, self-expanding, and has three bovine pericardial leaflets. The paddles are supposed to capture the native leaflets and secure them between the Fortis valve body and the paddles. This THV is delivered transapically with a 42 Fr system. First implants in eight patients showed an MR Grade 0 in three subjects, trace MR in one patient, and MR Grade 1+ in three patients. One patient had to be converted to conventional surgery. Four patients died in the 90 days follow-up.

The MitrAssist valve works with fixation of the transapically delivered valve at the papillary muscles. Chronic animal models showed no trauma to the leaflets, no leaflet adhesion, and no thrombus formation 35 days after implantation. First-in-human procedures are awaited. The Neovasc Tiara consists of a nitinol-based, self-expanding frame, bovine pericardium leaflets, and ventricular anchors to fix the valve onto the fibrous trigone and the posterior annulus. The valve is anatomically D-shaped. It is introduced by a 32 F sheathless system with a self-dilating tip via a transapical approach. First-in-human implants were successful in three patients in Canada: two of them suffered from an ischaemic cardiomyopathy and one from a dilated cardiomyopathy. There were no complications during the implants with MR Grade 0 in two patients and trivial MR in one patient postoperatively. All patients showed a lowering of the pulmonary pressure immediately post implant. A feasibility study with 30 patients is planned for the end of 2014.[35]

The CardiAQ TMVI system is made for both transfemoral and transapical access. It is placed intra- and suprannular to preserve the LV contractility and maximise the LVOT area. The anchoring frame is designed for annular attachment without the use of radial force and preservation of chordate and leaflets. It consists of a bi-level self-expanding nitinol frame.[36] Four successful first-in-human implants were undertaken in Copenhagen, Denmark, two of these patients died on days 3 and 9 due to Systemic Inflammatory Response System and pneumonia, and two patients are still alive with a good haemodynamic outcome and competent THV. A CE mark trial with 100 patients is scheduled for 2015.

COMMENTARY

Refinement of reconstructive techniques has made surgical MVR the reference treatment for patients with relevant MR. Surgery can be performed with low perioperative complication rates and excellent long term outcomes. Therefore, surgery may also be justified in asymptomatic patients. In Germany, rates of MVR as compared to prosthetic valve replacement have constantly increased. Minimally invasive techniques have further improved surgical results and have become the standard of care at specialised centres. Even though surgical MVR is an established therapeutic concept for patients with relevant MR, a large proportion of patients are denied surgery. Due to this fact, percutaneous strategies for MVR and MVI are brought forward after several years. Technologies currently under development can be classified by their anatomical approach. To date, only the percutaneous edge-to-edge approach is applied on a larger scale in clinical daily routine with the MitraClip device. Recently, MitraClip therapy has been incorporated into international guidelines for treatment of primary or secondary MR in inoperable or high-risk patients. Patient selection, performance of the procedure, and post-procedural care should be performed by an interdisciplinary team of cardiologists and cardiac surgeons. Several other technologies regarding percutaneous MVR have achieved first-in-man results. For comparable results of transcatheter MVR to surgical MVR a combination of these technologies will be required.

In the years following the introduction of an interventional MV programme at our centre, surgical MV activity has increased.[37,38] This increase in surgical caseload amounted to 32.2% from 2007-2012, and it was well above the national background, which showed an increase in caseload during the same timeframe of 10.2%.[39] The overall caseload of interventional and surgical MV patients increased by 71.3% from 2007-2012. In summary, it seems likely that, in addition to some crossover of patients initially considered for surgery but then deemed to be high-risk, MitraClip patients stem mainly from an 'on-top recruitment' process. Thus, addition of a MitraClip programme likely relieved undertreatment of patients with relevant MR.

The field of TMVI is also evolving quickly. With half a dozen devices under development at present and a few entering the clinical test stage, it may be just a matter of time until a THV for the mitral position will become commercially available. However, the anatomical challenges are prominent and results of a greater series of patients have to be awaited. In summary, the field of transcatheter MV therapies is quickly evolving with multiple new repair and replacement strategies in early clinical use. At present, all devices have to be restricted to inoperable patients or to compassionate use settings. However, once clinical proof of safety and efficacy have been demonstrated, extension to a broader patient spectrum seems likely. For a successful clinical programme, an interdisciplinary heart team of multiple specialities, but mandatorily including cardiologists and cardiac surgeons, is needed to ensure optimal patient care and careful evaluation of new techniques against the current surgical gold standard.

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