UNIVERSITÀ DEGLI STUDI DI PADOVA
Ph.D. Course Traslational Specialistic Medicine "G.B. Morgagni"
Curriculum: Cardiothoracic and Vascular Sciences

RESEARCH PROJECT TITLE:

AN INNOVATIVE DESIGN OF TRANSCATHETER IMPLANTABLE MITRAL VALVE PROSTHESIS.

Anatomy of the mitral valve in patients with functional mitral regurgitation and preliminary results of the implant in the animal model using quantitative 3D echocardiography and particle imaging velocimetry

Ph.D. STUDENT: PATRIZIA ARUTA
TUTOR: LUIGI BADANO

Summary

Abbreviations

3DE, three-dimensional echocardiography
AP, antero-posterior
ALPM, anterolateral-posteromedial
CC, commissural
CS, coronary sinus
DMR, degenerative mitral regurgitation
FMR, functional mitral regurgitation
HF, heart failure
IMR, ischemic MR
LA, left atrium
LV, left ventricle/ventricular
LVEF, left ventricular ejection fraction
LVOT, left ventricular outflow tract
MA, mitral annulus
MR, mitral regurgitation
MSCT, multi-slice computed tomography
MV, mitral valve
nIMR, non-ischemic mitral regurgitation
TA, trans-apical
Ta, tras-atrial
TS, trans-septal
TMVR, transcatheter mitral valve replacement
TEE, transesophageal echocardiography
TPE; transpericardial echocardiography
TTE, transthoracic echocardiography
VHD, valvular heart disease
vps, volumes per second

Abstract

Background: Transcatheter mitral valve replacement (TMVR) is a new therapeutic option for high surgical risk patients with mitral regurgitation (MR) and several prostheses are currently at different stages of development. Indeed, once prototypes of these prosthesis are designed, they need to undergo both bench testing and preclinical evaluation to test the performance and safety of the device and acquire useful information for guiding the secondary improvements. After this stage, if the prosthesis shows favourable results in terms of performance and safety, the manufacturer can apply for CE marking. In case of achievement of the CE mark, the clinical use can start in the European countries. The application of advanced echocardiography is useful not only in a preclinical experimental stage but results to be an irreplaceable tool in the proper selection of the treatment strategy with respect to the case-specific anatomic and functional mitral valve (MV) disease pattern and in the guidance of the correct bioprosthesis positioning and implantation during the procedure.

Aims: To describe the feasibility and advantage of 3D and contrast echocardiography in a preclinical study and report the acute hemodynamic results after implantation of a novel transcatheter self-expandable D-shape mitral bioprosthesis characterized by asymmetric stent and advanced mono-leaflet structure. In addition, we aimed to assess the MV geometry in patients with functional MR (FMR) that would potentially benefit from TMVR, focusing on the comparison between mitral annulus (MA) geometry of patients with ischemic (IMR) and non-ischemic mitral regurgitation (nIMR).

Methods: From May 2015 to August 2018, prosthesis prototypes were implanted under echocardiography guidance in 112 small-size healthy sheep using both trans-atrial (Ta) and trans-apical (TA) access. Multimodality imaging was used for animal selection and trans-pericardial echocardiography (TPE) was applied to obtain *humanized* image during intervention. Particle imaging velocimetry was used to assess intraventricular flow dynamics. We retrospectively selected 94 patients with severe FMR, both IMR and nIMR. 3D MA analysis was performed in early-diastole

and mid-systoleby using a recent, commercially-available software package. Measure of interest were MA dimensions and geometry parameters, left atrial and left ventricular volumes.

Results: 2D and 3D TPE was performed before and after implantation to measure MA dimensions (area: 6.4±0.8 cm^2, perimeter: 9.4±0.8 cm) and assess prosthesis alignment and function. The vast majority of implantations showed none or just trivial intra- (n=104, 93%) and peri-prosthesis leak (n=86, 77%) with good valve function (mean gradient 4 ± 3 mmHg). At particle imaging velocimetry, left ventricular vortex properties did not change after implantation.

In patients with severe FMR, 41 (43,6%) with IMR and 53 (56,4%) with nIMR, maximum MA 3D area (10.7±2.5 cm^2 vs 11.6±2.7 cm^2, p=0.124) and the best fit plane MA area (9.9±2.3 cm^2 vs 10.7±2.5 cm^2, p=0.135, respectively) were similar between IMR and nIMR. nIMR patients showed larger mid-systolic 3D area (9.8±2.3 cm^2 vs 10.8±2.7 cm^2, p=0.046) and perimeter (11.2±1.3 cm vs 11.8±1.5 cm, p=0.048), longer and larger leaflets, and wider aorto-mitral angle (135±10° vs 141±11°, p=0.011). Conversely, the area of MA at the best fit plane did not differ between IMR and nIMR patients (9±1.1 cm^2 vs 9.9±1.5 cm^2, p=0.063).

Conclusions: In the healthy sheep model, initial preclinical experience with a novel mono-leaflet transcatheter self-expandable mitral prosthesis showed that the TA implantation of the valve was feasible, safe, and supported by good hemodynamic results. The application of advanced echocardiography on an animal model was feasible and helpful in guiding the continuous refinements needed to enhance the development of this new concept of bioprosthesis.

Patients with ischemic and non-ischemic etiology of FMR have similar maximum dimension, yet systolic differences between the two groups should be considered to tailor prosthesis's selection.

Riassunto

Premesse: La sostituzione percutanea della valvola mitralica rappresenta una nuova opzione terapeutica per i pazienti con insufficienza mitralica (IM) ad alto rischio chirurgico. Attualmente molte protesi percutanee sono in differenti fasi di sviluppo. I prototipi valvolari, prima di ottenere il marchio CE ed iniziare l'uso clinico, devono essere sottoposti a test su animale per raggiungere il design finale. Inoltre, la valutazione della geometrica valvolare mitralica è fondamentale per il successo procedurale e l'ecocardiografia transtoracica 3D rappresenta un utile strumento di screening.

Scopi: Valutare la fattibilità dell'impianto e i risultati emodinamici in acuto di una nuova bioprotesi percutanea auto-espandibile caratterizzata da una forma a D con stent asimmetrico e da un unico lembo. Valutare la geometrica della valvola mitralica in pazienti con IM funzionale (IMF) che potrebbero potenzialmente beneficiare della sostituzione percutanea della valvola mitralica, confrontando i pazienti con IMF secondaria a cardiopatia ischemica (IMF-I) e non-ischemica (IMF-nI).

Metodi: Da Maggio 2015 ad Agosto 2018 sono stati impiantati prototipi della nuova bioprotesi su 112 ovini sani di piccola taglia usando l'approccio trans-atriale (Ta) e trans-apicale (TA). La selezione degli ovini è avvenuta mediante tomografia computerizzata ed ecocardiografia, mentre l'impianto è stato guidato tramite ecocardiografia trans-pericardica (ETP) che ha permesso di ottenere immagini *"umanizzate"*. Inoltre, l'analisi della velocità delle particelle è stata utilizzata per valutare la dinamica del flusso intracavitario prima e dopo impianto della bioprotesi.

Sono stati retrospettivamente selezionati 94 pazienti con IMF severa. L'analisi 3D dell'AM è stata eseguita su immagini 3D dedicate, utilizzando un nuovo software d'analisi disponibile in commercio, in due momenti del ciclo cardiaco (protodiastole e mesosistole). Sono state misurate le dimensioni e la geometria dell'AM e i volumi atriali e ventricolari sinistri.

Risultati: ETP 2D e 3D è stata utilizzata per misurare le dimensioni dell'AM nel modello ovino (area: 6.4 ± 0.8 cm2, perimetro: 9.4 ± 0.8 cm) e per valutare l'allineamento ed il funzionamento della

protesi. La maggioranza degli impianti hanno mostrato nessuna o solo minima insufficienza intra- (n=104, 93%) e peri-protesica (n=86, 77%) ed un buon funzionamento della protesi (gradiente medio 4 ± 3 mmHg). Inoltre, all'analisi della velocità delle particelle, le proprietà dei vortici del ventricolo sinistro rimangono invariati dopo l'impianto.

Nei pazienti con IMF severa, 41 (43.6%) con IMF-I e 53 (56.4%) con IMF-nI, l'area massima 3D dell'AM (10.7±2.5 cm^2 vs 11.6±2.7 cm^2, p=0.124) ed a livello del *best fit plane* (9.9±2.3 cm^2 vs 10.7±2.5 cm^2, p=0.135, rispettivamente) sono simili tra i pazienti con IMF-I e IMF-nI. In mesosistole, i pazienti con IMF-nI mostrano una maggiore area 3D (9.8±2.3 cm^2 vs 10.8±2.7 cm^2, p=0.046) e perimetro (11.2±1.3 cm vs 11.8±1.5 cm, p=0.048) con lembi più lunghi e grandi, ed un più ampio angolo aorto-mitralico (135±10° vs 141±11°, p=0.011). Mentre l'area dell'AM a livello del *best fit plane* non differisce tra i pazienti con IMF-I e IMF-nI (9±1.1 cm^2 vs 9.9±1.5 cm^2, p=0.063).

Conclusioni: L'iniziale esperienza pre-clinica della nuova bioprotesi mono-lembo autoespandibile, ha evidenziato che l'impianto della valvola tramite approccio TA è fattibile e sicuro con un buon risultato emodinamico. L'utilizzo di metodi ecocardiografici avanzati su modello animale è stato fattibile ed ha supportato il continuo sviluppo di un nuovo concetto di bioprotesi. I pazienti con IMF ad eziologia ischemica e non-ischemica hanno simili dimensioni massime dell'AM; le differenze sistoliche nella geometria dell'AM dovrebbero essere prese in considerazioni per l'accurata selezione delle protesi.

Introduction

Mitral regurgitation (MR) represents the second most frequent valvular heart disease after aortic valve stenosis in Europe.[1] Among patients with moderate and severe MR, 30% are affected by functional MR (FMR) with a high prevalence of the ischemic etiology[2].

Despite the clinical indication, 49% of patients with MR are denied for surgery due to advanced age, reduced ejection fraction and multiple comorbidities[3] and among them the vast majority is represented by patients with FMR.[4]

If left untreated, MR associates with poor prognosis and , progressive left ventricular dysfunction and heart failure (HF).[5] Severe MR in patients with heart failure is associated with 20% and 50% mortality rates at 1-year and 5-year follow-up, respectively.[4]

In the last decade, minimally invasive procedures simulating surgical techniques have been developed to extend the therapeutic options for this high surgical risk patients and transcatheter mitral valve replacement (TMVR) is one of the recent most promising options.[6-8]

Mitral valve (MV) geometry quantification is of paramount importance for the success of TMVR, and transthoracic (TTE) three-dimensional echocardiography (3DE) is a useful tool to select the patients with the highest likelihood of uncomplicated implant.[9]

It has been previously reported that MV geometry may be different in ischemic and non-ischemic FMR. Indeed, in patient with ischemic MR (IMR), regional wall motion abnormalities and left ventricular (LV) remodeling[10] are more often associated with asymmetric mitral annulus (MA) dilatation.[11] Conversely, in non-ischemic MR (nIMR) global LV remodeling leads to symmetric MA dilatation.[12] Yet, MV geometry in FMR has been mainly compared with organic MR, and only few small echocardiographic studies analyzed MV geometry differentiating between IMR and nIMR.[11-14] However, none of them provided MA geometry characterization framed to pre-procedural screening for TMVR.[9]

Epidemiology of mitral regurgitation

Valve heart disease is becoming an increasing public-health problem. Data from the Euro Heart Survey showed that among the isolated native left-sided valve diseases, aortic stenosis was the most frequent (n=1197, 43.1%) followed by MR (n=877, 31.5%), aortic regurgitation (n=369, 13.3%), and mitral stenosis (n=336, 12.1%).[1] Large part of this patients was affected by severe valve disease (n=809, 67.6% - aortic stenosis; n=546, 67,6% - MR; n=230, 62.3% -aortic regurgitation; n=232, 69% -mitral stenosis). The most frequent etiology for aortic valve disease was degenerative. In MR, degenerative etiology was also most common (61.3%) followed by rheumatic disease (14.2%), then ischemic (7.3%); endocarditis was present in 3.5%. Most cases of mitral stenosis were rheumatic in origin (85.4%). Overall, the patients with valve heart disease are often elder with a high frequency of cardiovascular risk factors and comorbidities.

Nkomo and colleagues reported data about the burden of valve heart disease in the US population.[15] Among the 11911 echocardiograms in the pooled population-based study, valve heart disease was detected in 615 (5.2%, 95% CI 4.8%–5.6%) participants. MR was the most common valve heart disease, while mitral stenosis the least frequent. Similar to the Euro Heart survey, the prevalence of valve disease rose strikingly with advancing age. **(Figure 1)**

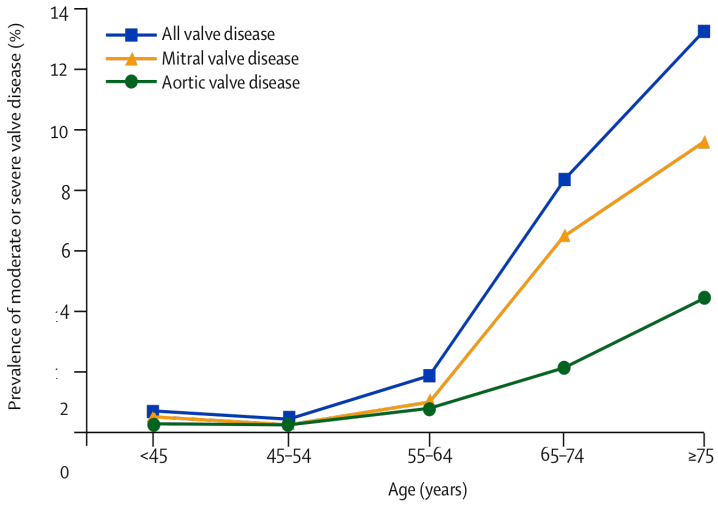

Figure 1 Prevalence of valve heart diseases by age.[15]

Moreover, survival of participants with valve disease was significantly reduced compared with those without disease. **(Figure 2)**

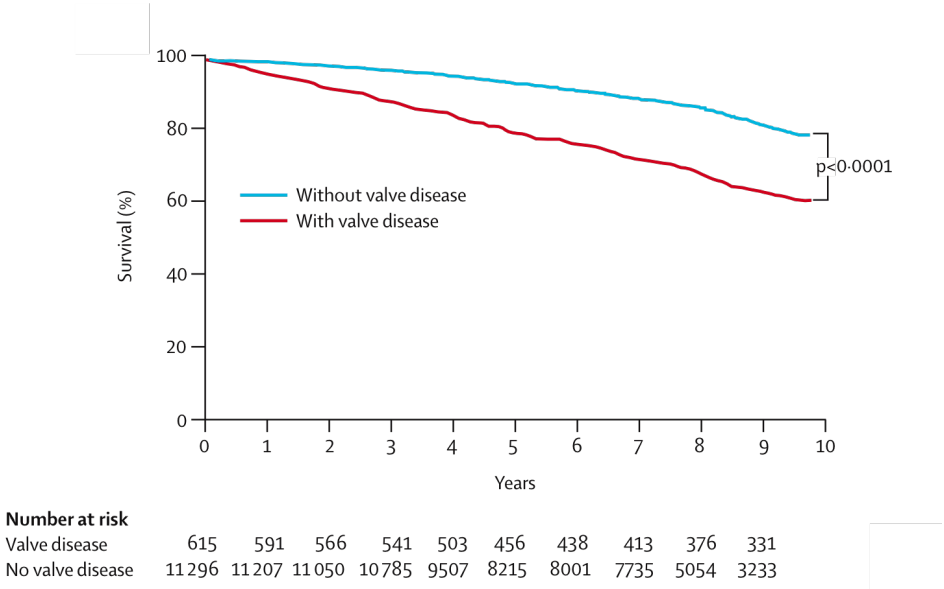

Figure 2 Survival after detection of moderate or severe valve heart disease.[15]

Mirabel and colleagues used the Euro Heart Survey data to estimate the actual proportion of symptomatic patients with severe MR in whom the decision not to operate was taken.[3] Of the 546 patients with severe MR, 396 were symptomatic but in only the 51% of them (n=203) was decided to operate. Combined coronary artery bypass grafting occurred in 39 symptomatic patients (29%) treated by surgery during the survey period (n=135) and in 15 of the 18 (83%) patients who underwent surgery for ischemic MR. Surgery was denied more frequently in older patients, in those with congestive HF, reduced left ventricular ejection fraction (LVEF) and with comorbidity. Patients with ischemic MR were more often considered for surgery than those with non-ischemic disease, in particular degenerative MR. Mirabel and colleagues suggested that coronary disease mostly drove the indication to surgery in patients with ischemic MR, since the majority of patients with ischemic MR underwent intervention associated with coronary artery bypass grafting.

The burden of MR in Europe was recently assessed by the EuMiClip (European Registry of mitral regurgitation) group.[2] From a total of 63463 consecutive echocardiographic studies performed in the participant hospitals during the recruitment period (3 months), 24.4% of patients had MR of any

degree. **(Figure 3)** In the subgroup of moderate and severe MR (n=3309), there were 1806 (55.1%) patients with primary MR and 1010 (30.1%) patients with secondary MR. A mixed etiology of MR was described in 14.1% of the studies. **(Figure 4)** Degenerative disease was the most common etiology of primary MR (59.8%), followed by Barlow disease (14.4%), rheumatic disease (10.1%), endocarditis (1.6%), and congenital disease (1.5%). Additionally, ischemic was the most common etiology of secondary MR, present in 51.4% of cases while about 31.9% of patients had dilated cardiomyopathy.

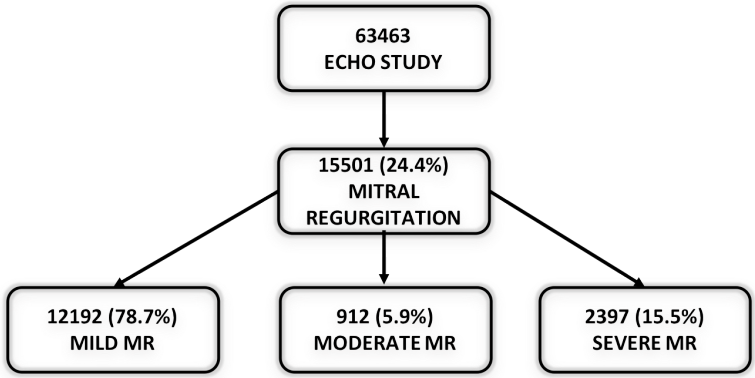

Figure 3 Distribution of patients with mitral regurgitation in the EuMiClip registry. [2]

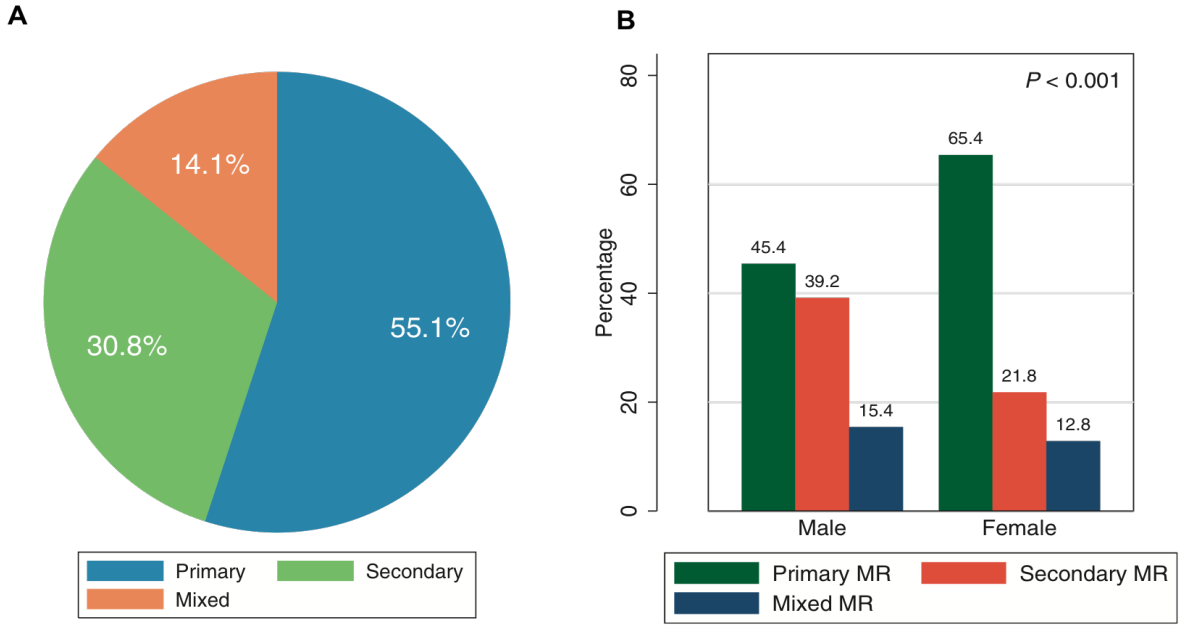

Figure 4 Prevalence of mitral regurgitation forms. *(A) Prevalence in patients with moderate and severe mitral regurgitation. (B)Mitral regurgitation forms by gender.* [2]

In the EuMiClip study population, 70% of patients with severe primary MR met the criteria for intervention according to current guidelines,[16] while in the secondary MR group only 13.1% where eligible for isolated surgical correction. Severe left ventricular dysfunction was found in 38.8% of patients with significant secondary MR. Furthermore, the proportion of patients aged over 80 years old in this group stood at 25.7 %.

Current surgical therapeutic options for patients with functional mitral regurgitation

In case of organic (primary) MR, open-heart surgical treatment is the recommended treatment for patients with severe symptomatic MR despite optimal HF medical therapy, reduced LVEF, atrial fibrillation secondary to MR or pulmonary hypertension (>50mmHg).[16] In case of FMR, the optimal treatment is more controversial due to the paucity of data and the significant rates (up to 20%) of recurrent regurgitation within the first year after surgery.[17] Moreover, recurrence of MR dramatically increase the onset of HF, atrial fibrillation, and re-hospitalization.[18] Against this background, only 15% of FMR patients are referred for surgical treatment.[19] Surgery is indicated when associated with coronary artery bypass graft procedure or in cases when optimal medical therapy and resynchronization have no or minimal results in improving the symptomatology and the patient has a low surgical risk.[16]

Current guidelines,[16] however, do not specify whether to repair or replace the mitral valve, because conclusive evidence is lacking, without clear superiority of a strategy over the other.[18] Clinical studies have suggested that valve repair is associated with lower perioperative mortality,[20-22] whereas valve replacement provides better long-term correction of the regurgitation with a lower risk of recurrence.[18]

The Cardiothoracic Surgical Trials Network (CTSN) conducted a multicenter, randomized trial to evaluate the relative benefits and risks of mitral-valve repair versus chordal-sparing replacement, with or without coronary revascularization, in patients with severe ischemic MR.[18] Among the 251 patients that underwent randomization, 126 to mitral-valve repair and 125 to mitral-valve replacement, 86.1% had a concomitant coronary artery bypass grafting. All patients undergoing mitral-valve repair received complete annuloplasty rings. At 12 and 24 months of follow-up left ventricular reverse remodeling, assessed by left ventricular end-systolic volume index, and survival were comparable between treatment groups. **(Figure 5)**

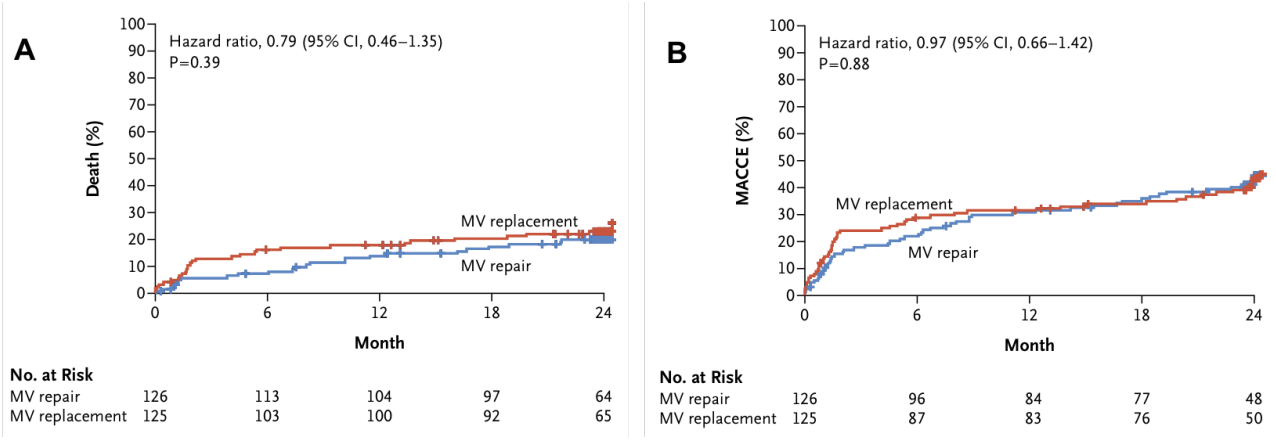

Figure 5 Time-to-Event Cumulative Incidence Curves of Death and Major Adverse Cardiac or Cerebrovascular Events (MACCE). *(A) Incidences of patients who died in the mitral valve repair group and in the mitral valve replacement group at 2 years. The most frequent underlying causes of death were multisystem organ failure (20.8%), heart failure (17.0%), and sepsis (13.2%). (B) Incidences of the composite endpoint of safety events at 2-year follow-up. MACCE was defined as death, stroke, hospitalization for HF, worsening HF heart failure, or mitral valve reintervention.[23]*

At 2-year follow-up, the proportion of patients with recurrent moderate or severe MR was significantly higher in the repair group than in the replacement group (58.8% vs 3.8%, p<0.001).[23] **(Figure 6)** The high rate of recurrence of MR in the repair group did not correspond to significant variations in the composite end point of major adverse cardiac or cerebrovascular events, in the

quality of life, or in the functional status at 12 and 24 months.[18,23] However, in the repair group there was a significant increase in HF–related adverse events and cardiovascular-cause readmission. On the other hand, patients in the repair group who did not experience recurrent mitral regurgitation showed significant reverse remodeling and better quality of life.[23]

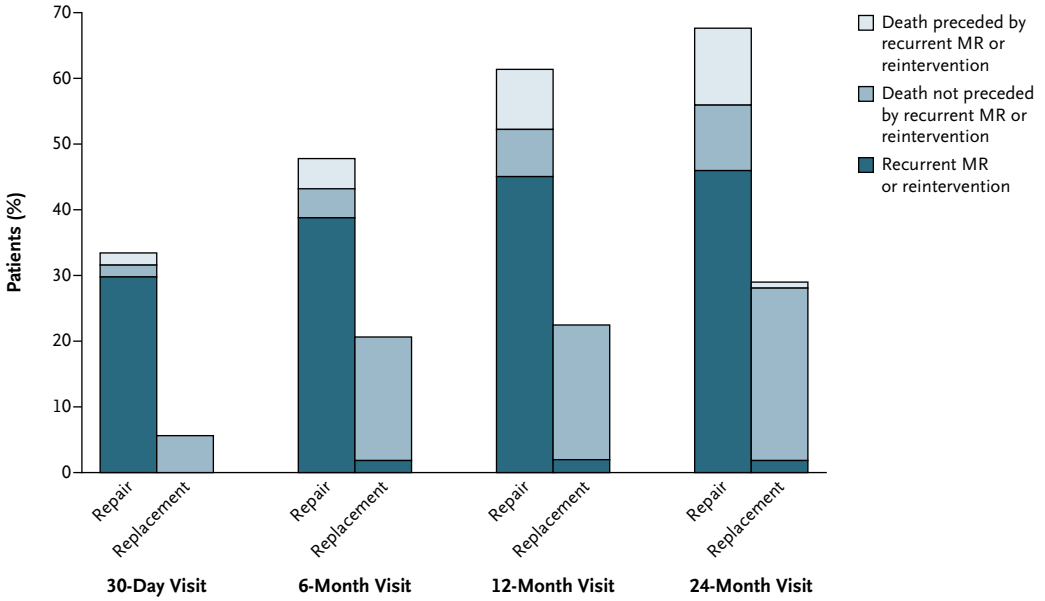

Figure 6 Cumulative Failure of Mitral-Valve Repair or Replacement. *Failure of the intervention was defined as death, moderate or severe mitral regurgitation (MR) as seen on transthoracic echocardiography, or mitral valve reintervention.*[23]

Transcatheter interventional techniques for functional mitral valve regurgitation

Transcatheter repair techniques can be categorized according to the different type of approach[24]: 1) leaflet repair, 2) direct or indirect annuloplasty, 3) chordal implantation. To date, five devices designed for MV repair have received the *Conformité Européenne* (CE) mark approval. Four of them are used for FMR treatment, though anatomic and clinical indications are limited to specific subsets and the procedure generally does not allow achieving an almost complete reduction of the regurgitation in all patients, with >10% of them having at least moderate residual MR.[25,26] To overcome these limitations and meet the needs of wider applicability and more predictable reduction in MR, TMVR has emerged as a new promising therapeutic option. Although, there are important challenges to overcome in the development of this new technology due to the complex MV apparatus anatomy, the need for large and highly flexible delivery catheters and the wide spectrum of MV disease, TMVR represents the new frontier of intervention and advances of recent years were substantial. Several prostheses are currently at different stage of investigation and more than 150 patients have already been implanted in various early feasibility studies.

Transcatheter mitral valve repair system

1) Leaflets repair

MitraClip

The MitraClip (Abbott Vascular, Abbott Park, IL, USA) system replicates the Alfieri's double orifice technique for MV repair. **(Figure 7)** The device is approved in Europe for treatment of FMR[27] and degenerative MR . Current European guidelines consider the MitraClip system as a therapeutic option in high or prohibitive surgical risk patients (Recommendation class IIb, Level of evidence C) who meet the anatomical criteria of suitability.[16] **(Table 1)**

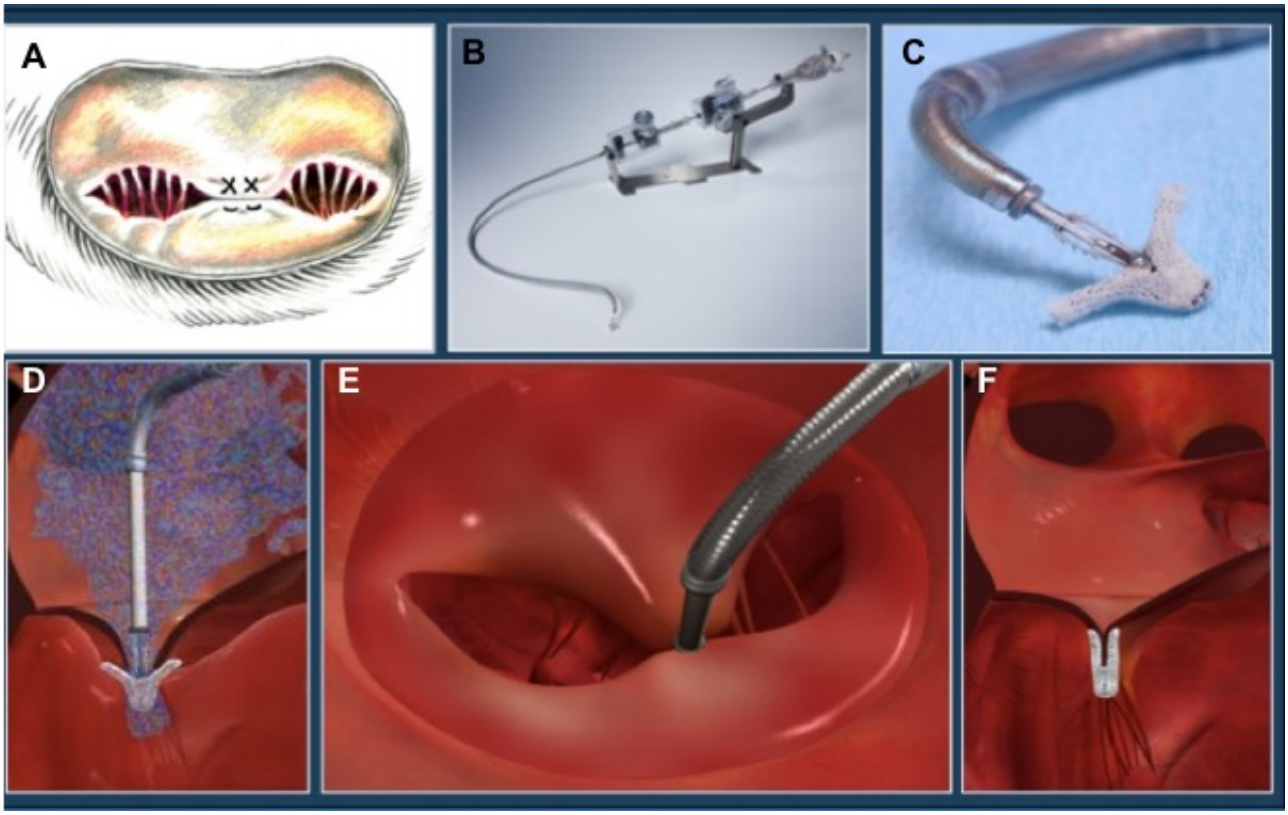

Figure 7*. *MitraClip system. *(A) Alfieri stitch surgical technique; (B) Delivery catheter of MitraClip system; (C) Mitraclip; (D-F) Essential phases of implantation: (D) alignment of the mitraclip, (E) double orifice after clip implantation, (F) MitraClip released with leaflets inside.*[28]

Almost a total of 50.000 MitraClip interventions have been performed worldwide and the procedure has been extensively reported after the first clinical use, in 2003.[29] Using femoral vein access, the trans-septal (TS) puncture is performed at the level of fossa ovalis by 24-F steerable guide catheter. After the delivery system is introduced in the left atrium (LA), the MitraClip, a two cobalt-chrome arms device with 4 mm opening width, is aligned perpendicularly to the MV coaptation line and moved then into the left ventricle [10] in order to grasp and grip the two edges of the MV leaflets. All MitraClip procedures are performed under fluoroscopic and transesophageal echocardiographic (TEE) guidance and during general anesthesia.

After the first release, an improved version of the device, named MitraClip NT, has been developed for a deeper leaflet insertion and more stable fixation. Recently, the latest version of the device, the MitraClip XT_R, was released and its performance is currently investigated in the MitraClip EXPAND study (NCT03502811, www.clinicaltrials.gov). In comparison with the MitraClip NT, the

newer system has longer clip arms and longer grippers, facilitating the grasping of MV leaflets. **(Figure 8)**

Table 1. Indications for percutaneous edge-to-edge treatment of mitral regurgitation. *Adapted from Boekstegers et al*[10]**.**

Optimal valve morphology	Conditionally suitable valve morphology	Unsuitable valve morphology
Central pathology in segment 2	Pathology in segment 1 or 3	Perforated mitral valve leaflet or cleft
No leaflet calcification	Mild calcification outside the grip zone of the clip system, ring calcification, post annuloplasty	Severe calcification in the grip zone
Mitral valve opening area >4 cm^2	Mitral valve opening area >3 cm^2 with good residual mobility	Haemodynamically significant mitral stenosis (valve area <3 cm^2, mean gradient ≥5 mm)
Mobile length of the posterior leaflet ≥10 mm	Mobile length of the posterior leaflet 7-<10 mm	Mobile length of the posterior leaflet <7 mm
Coaptation depth <11 mm	Coaptation depth ≥11 mm	
Normal leaflet strength and mobility	Leaflet restriction in systole (Carpentier III B)	Rheumatic leaflet thickening and restriction in systole and diastole (Carpentier III A)
Flail width <15 mm and flail gap <10 mm	Flail width >15 mm only with a large ring width and the option for multiple clips	Barlow's syndrome with multisegment flail leaflets

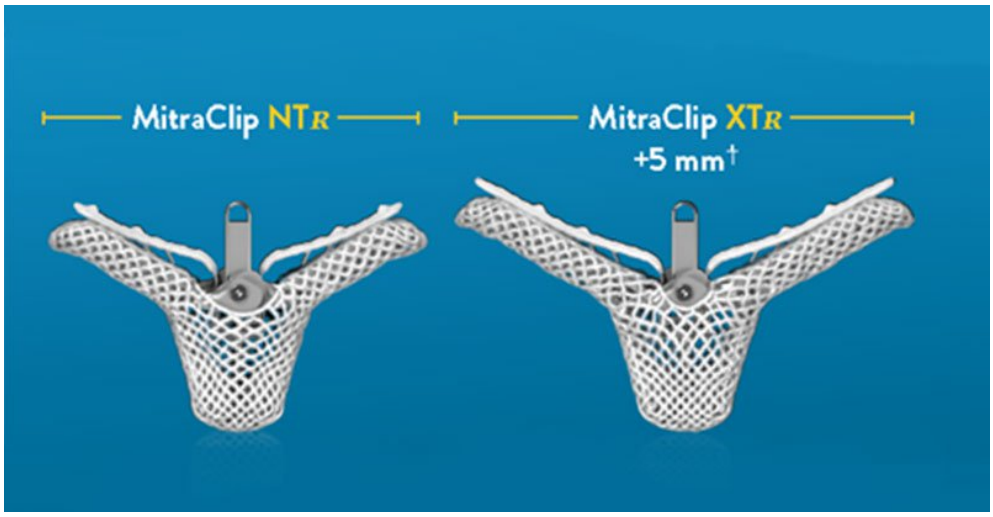

Figure 8. MitraClip NT_R and XT_R

Several randomized controlled trial (RCT) and post-marketing registry have been conducted in the recent years with the aim of assessing the effectiveness and safety of the MitraClip system. The

EVEREST (Endovascular Valve Edge-to-edge REpair Study) phase I, a non-randomized feasibility trial, proved that the procedure had acceptable effectiveness and safety at 6-month follow-up.[29] The EVEREST II study, a multicentre open-label randomized clinical trial comparing the MitraClip procedure with MV surgery (repair or replacement) in operable patients,[30] showed at 5-year follow-up a stable MR reduction and LV remodelling after MitraClip application, without significant difference in mortality between the two groups.[31] However, the net effectiveness resulted to favor the surgical arm (44.2% vs 64.3%,p=0.01) because of a higher prevalence of MR grade ≥2 and reintervention in the transcatheter group. Device dysfunction with subsequent need for re-intervention occurred mainly within the first 6 months.[31] Beyond this time period there were no significant differences between the two arms in terms of freedom from surgery.[31]

The results of the following two more recent trial have been disclosed in the last months: the MITRA-FR trial[32] (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and the COAPT trial[33] (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation). Both trials were designed to evaluate the clinical efficacy and safety of percutaneous mitral-valve repair in addition to medical treatment in patients with heart failure and severe secondary MR compared with optimal medical therapy. In the MITRA-FR trial[32], a total of 307 patient with severe secondary MR were randomized to percutaneous mitral valve repair and optimal medical therapy (n=152, intervention group) or optimal medical therapy alone (n=152, control group). At 1-year follow-up, the incidence of death or unplanned hospitalization for HF did not significantly differ between the two arms.[32] **(Figure 9)** Despite the good procedural success observed, with 76.4% of MitraClip patients showing MR regurgitation 0+ to 1+ at the time of hospital discharge, it was not possible to confirm sustained results of the transcatheter intervention for the considerable amount of missing echocardiographic and clinical data at follow-up.

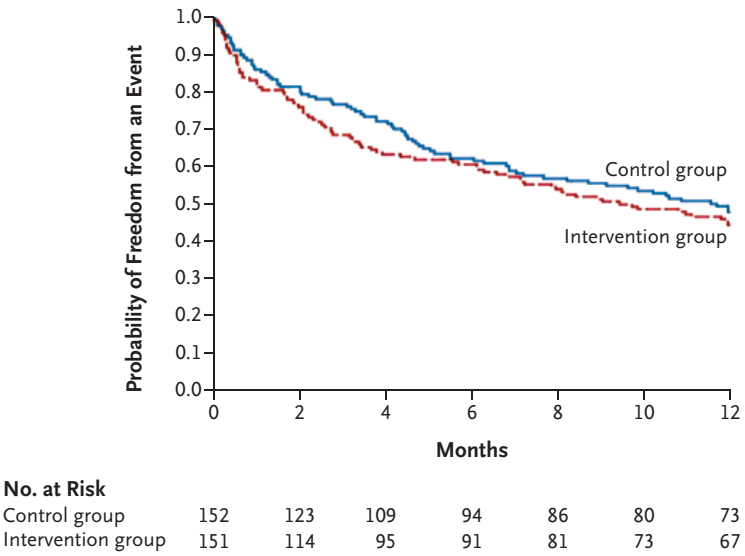

Figure 9. Kaplan–Meier estimates of survival without a primary outcome event of MITRA-FR. *Shown are estimates of the probability of survival without a primary out-come event (death from any cause or unplanned hospitalization for heart failure) in the two trial group.*[32]

In the COAPT trial[33] 614 patients were enrolled at 78 centers in the United States and Canada and randomized in a 1:1 ratio to MitraClip associated with optimal medial therapy (n=302) or optimal medial therapy alone (n=312). At 24 months of follow-up, the total number of hospitalizations for HF and death from any causes were significantly lower in the device group compared to the control group. **(Figure 10 and 11)**

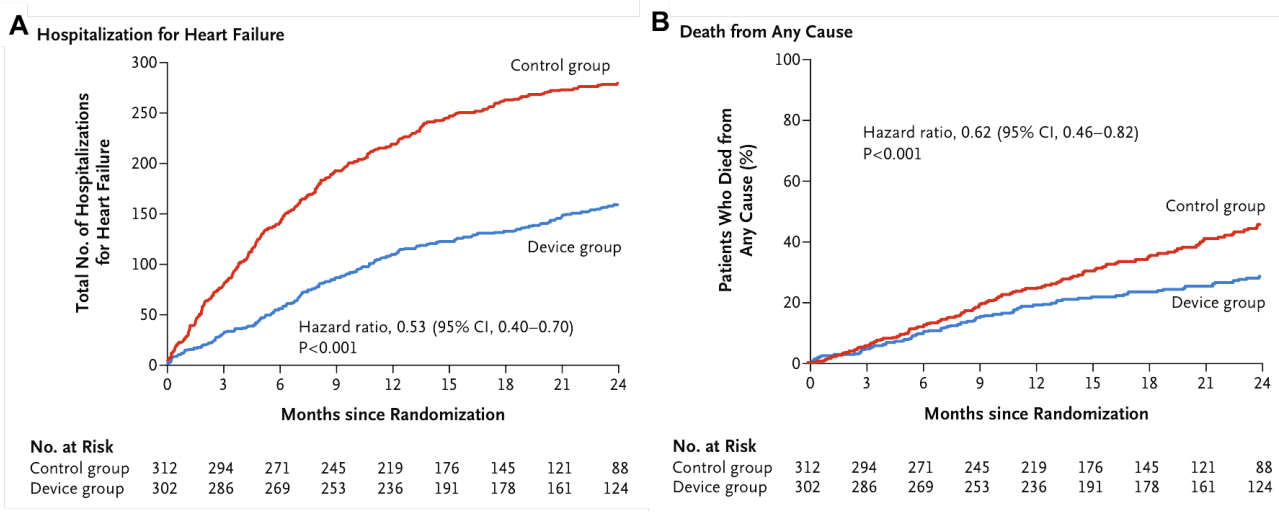

Figure 10 Repeat hospitalization due to heart failure and death in the COAPT trial. *A) Panel A shows the 24-month comparison between cumulative incidences in the primary effectiveness endpoint of any hospitalization for heart failure. B) Panel B shows the 24-month comparison between cumulative incidences in all-cause mortality.*[33]

The benefits were consistent across several subgroups, including patients who had ischemic and non-ischemic cardiomyopathy and were independent of MR grade, LV volume, and LV function at baseline. The number needed to treat to prevent 1 hospitalization for heart failure within 24 months was 3.1 (95% CI, 1.9 to 7.9); the number needed to treat to save 1 life within 24 months was 5.9 (95% CI, 3.9 to 11.7).

Two main differences could partially explain the opposite results of the two trial: patient's selection and length of follow-up. Despite in both trials were included only patients with severe MR, in the COAPT trial severe LV dilatation was an exclusion criterion (LV end-systolic diameter >70 mm). Moreover, in the COAPT trial the lower mortality became apparent after 1 year after from the intervention, which is when the MITRA-FR trial follow-up was terminated.

The three largest published European registries are: the German registry (TRAMI, TRAnscatheter Mitral valve Implantation) including 828 patients, the ACCESS-EU (MitraClip Therapy Economic and Clinical Outcome Study in Europe) including 567 patients, and the TCVT (TransCatheter Valve Treatment) sentinel pilot registry including 628 patients.[34,35,36] When compared with the EVEREST trial, data from these registries demonstrated a higher procedural success (97%, 91.%, and 95% in the TRAMI, ACCESS-EU, and TCVT registries respectively compared with 77% in the EVEREST II trial) and a lower prevalence of MV reintervention (8.5%, 9.7%, and 3.8% in the TRAMI, ACCESS-EU, and TCVT registries respectively compared with 21% in the EVEREST II trial). However, there was also a higher incidence of mortality in the observational studies both at 30 days (4.5% and 3.4% in the TRAMI and ACCESS-EU registries respectively vs 1% in the EVEREST II trial) and at 1 year (20.3%, 17.3%, and 15.3% in the TRAMI, ACCESS-EU, and TCVT registries, respectively vs 6.1% in the EVEREST II trial)[31,34,35,36].

Several trials testing the MitraClip system are still ongoing. The COAPT CAS — the extension of COAPT trial — is focusing on the use of MitraClip NT systems in patients with FMR and HF. The MITRA-CRT (MitraClip in Non-Responders to Cardiac Resynchronization Therapy;

NCT02592889, www.clinicaltrials.gov) trial has the main objective of comparing the efficacy and safety of MitraClip and optimal medical therapy (OMT) versus OMT alone in patients with symptomatic FMR without response to CRT. The MATTERHORN (Mitral vAalve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN; NCT02371512, www.clinicaltrials.gov) trial compares the MitraClip intervention vs the reconstructive/replacement surgical therapy in patients with FMR associated with LV dysfunction and increased risk for surgery.

2) Annuloplasty devices

Annuloplasty is the most common surgical repair technique for FMR which aims to reduce the MA dimensions. Different devices have been developed to obtain similar objective by using direct or indirect - through the coronary sinus - transcatheter approach, but results on MR severity and LV reverse remodeling were moderate and heterogeneous. As the MitraClip procedure, most of these procedures are performed under fluoroscopic and TEE guidance and during general anesthesia.

A. Direct annuloplasty system

CardioBand system

The CardioBand System (Edwards Lifesciences, Irvine, CA, USA) is a dacron band designed for supra-annular fixation of the mitral valve. It consists of a flexible incomplete polyester sleeve, that is secured to the posterior region of the MA by multiple helix anchors and fixed from the anterolateral to posteromedial commissure, and a contraction wire that is connected to the size adjustment tool allowing the contraction of the system to cinch the annulus. Transfemoral venous access by a 25-F TS steering sheath is demanded for the procedure. **(Figure 11)**

The first-in-human CE approval trial included 45 patients with moderate to severe FMR (NCT01841554, www.clinicaltrials.gov) showing a technical success rate of 93.6%, with significant decrease of the anteroposterior diameter (21.1%, from 36.8±4.8 mm to 29.0 ± 5.5 mm) and MR grade ≤ 2 in 88%. The CardioBand received CE mark approval in September 2015. There were two in-

hospital deaths, both adjudicated as unrelated to the device or procedure, one due to hemorrhagic stroke and the other one to elective MV replacement and tricuspid annuloplasty intervention for device malfunction.[37] Among serious adverse events, there were two recurrent MR due to partial anchor detachment in the early phase of the study.[37] At 6 and 12-month follow up, respectively 86% (n=22) and 94% (n=17) of patients showed MR ≤2 and 82% (n=22) and 68% (n=18) had NYHA class I-II.[38] In August 2016, the REPAIR (transcatheteR rEPair of mitrAl Insufficiency With caRdioband System; NCT02703311, www.clinicaltrials.gov) efficacy trial, has started and is currently enrolling patients with severe FMR and HF symptoms to test the decrease in MR grade and symptoms improvement, as well as to evaluate the safety of the CardioBand system in the post-marketing setting.

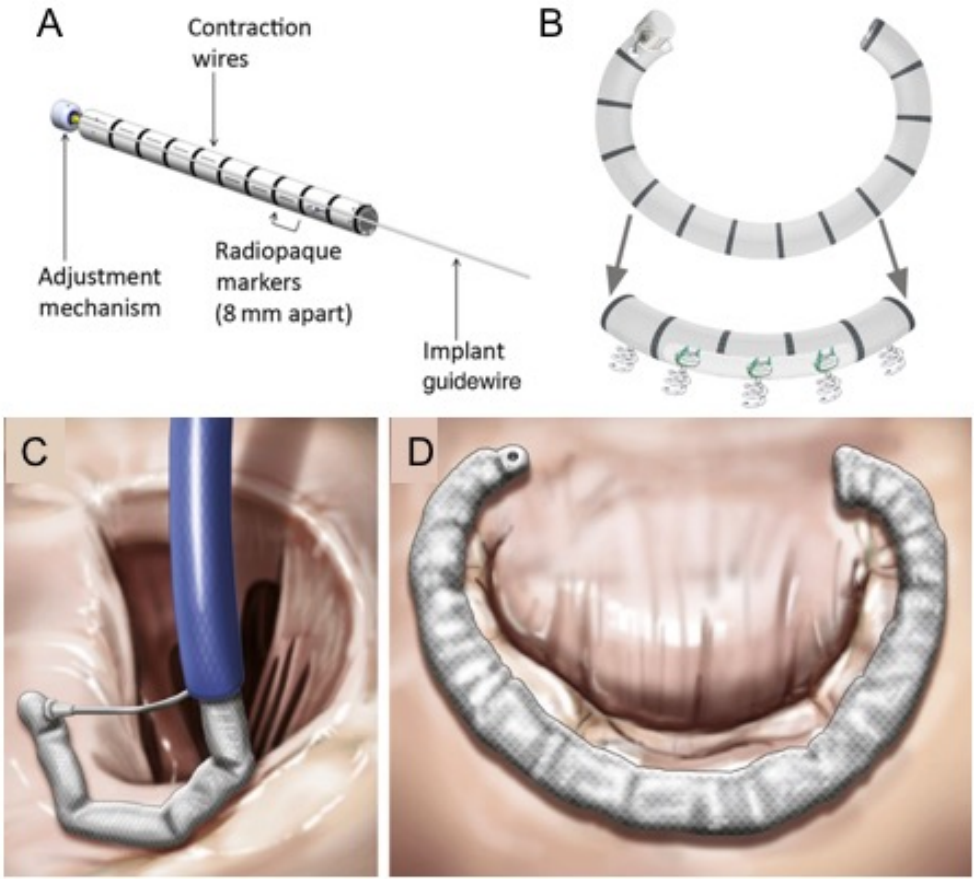

Figure 11 CardioBand system. *(A) CardioBand system before implantation and (B) after implantation. The implant is a polyester sleeve with radiopaque markers spaced 8 mm apart. (C) The guide catheter delivering the annuloplasty ring in segments. (D) Final annuloplasty ring encircling the posterior leaflet.*

AccuCinch system®

The AccuCinch® System (Ancora Heart, Santa Clara, CA, USA) is the first ventriculoplasty device that addresses dilated cardiomyopathy of either ischemic or non-ischemic etiology, aiming to obtain reverse LV remodeling and reduction in MR severity. It is made of 12 to 16 self-expandable nitinol anchors and 6-7 nitinol force distribution members. The device is implanted through a retrograde approach, using a 18-F femoral artery sheath, in the posterior sub-annular LV myocardium.[39] Anchors are placed to create a 220° arch that surrounds the posterior leaflet of the MV. The cinching force applied to the basal LV free wall is transmitted to the MA, reducing its dimension. **(Figure 12)**

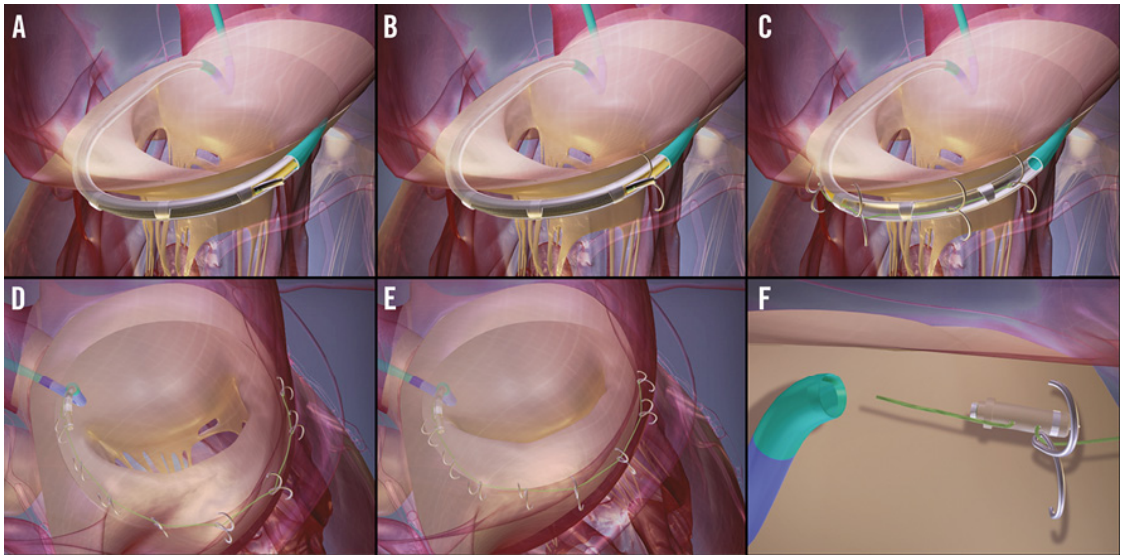

Figure 12 Delivery of the Accucinch System. *The subannular space is accessed using the guide catheter and the modular guide tunnel (MGT) positioned over a guidewire (A). The inner and outer MGT windows are aligned and anchors delivered (B). The inner MGT window is progressively withdrawn and subsequent anchors delivered (C) until the complete number of anchors has been delivered, joined by the cinch cable (D). The cinch cable is then progressively tightened to reduce the basal left ventricular and mitral annulus dimensions (E). The cinch cable is then locked to maintain the tension and cut (F) prior to removal of the guide catheter and MGT.[39]*

There were two studies addressing the feasibility, safety and efficacy of AccuCinch® System, involving around 10 patients: LVRECOVER (Left Ventricular Reshaping of the Mitral Apparatus to Reduce Functional Mitral Regurgitation and Improve Left Ventricular Function Trial; NCT02153892, www.clinicaltrials.gov) and LVRESTORESA (Percutaneous Left Ventricular Reshaping to Reduce Functional Mitral Regurgitation and Improve LV Function; NCT01899573,

www.clinicaltrial.gov) trials, both with promising results. An expansion of the feasibility study has been approved in US and recruitment should start soon.

Mitralign System

Mitralign Transcatheter Annuloplasty System (Mitralign Inc., Tewksbury, MA, USA) replicates the surgical annular plication using a set of devices placed at the level of posterior annulus, through the LV. Two pairs of polyester pledgets are delivered at the sites of P1 and P3 and then pulled together to decrease the annular circumference. After achieving the desired result, the plication is locked.[40] **(Figure 13).** The procedure is performed using a 14-F catheter transfemoral retrograde approach under real time 3D and 2D TEE.

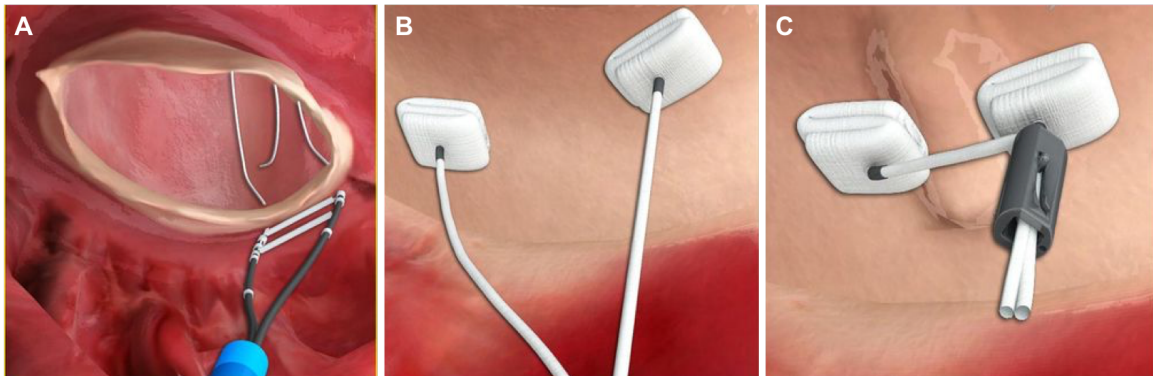

Figure 13. MITRALIGN System*. (A) Bident catheter and wire crossing mitral annulus (B) Pledget delivery (C) Pladget plication and lock*

The ALIGN study (Mitralign Percutaneous Annuloplasty System for Chronic Functional Mitral Valve Regurgitation; NCT01740583, www.clinicaltrials.gov) included 71 patients with FMR grade ≥2. Device success rate was 70.4% and no intraprocedural death occurred. Thirty-day (n=45) and 6-month (n=41) incidences of all-cause mortality, stroke, and myocardial infarction were 4.4%, 4.4%, and 0% and 12.2%, 4.9%, and 0% respectively. At 6 months, non-urgent MV surgery was performed in 1 patient (2.4%) and non-urgent percutaneous repair in 7 patients (17.1%). The results of 6-month follow-up showed overall signs of reverse LV remodeling with reduction in LV end-diastolic dimension and LV volume, significant reduction of MA dimensions, both anteroposterior

and mediolateral diameters, and MR grade with a significant improvement in coaptation length, decreased MV tenting area, and improvement in NYHA functional class.[41] Following these results, the Mitralign received CE mark approval in February 2016 for treatment of FMR. The Mitralign system has been also applied for the treatment of functional tricuspid regurgitation (SCOUT I Early Feasibility Study; NCT02574650, www.clinicaltrials.gov; and the SCOUT II CE Mark Study; NCT03225612, www.clinicaltrials.gov).[42,43]

B. Indirect annuloplasty system

The coronary sinus (CS) can be a favorable site for the performance of transcatheter MV repair because of its easy accessibility and anatomic proximity to MA. However, the distance between MA and CS is variable, smaller at the level of anterolateral commissure (distal CS) and larger at the level of posteromedial commissure (proximal CS), and increases with MR grade.[44] In addition, an anatomical issue to take into account when considering the indirect annuloplasty is the close spatial relationship between CS and left circumflex coronary artery with a potential risk of vessel compression during the procedure.

The CARILLON® Mitral Contour System®

Different devices for indirect annuloplasty have been developed with unfavorable results and the studies have been stopped at various preclinical or clinical stage. The CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc., Kirkland, WA, USA) is the only device that received CE mark approval to date. It is composed of two self-expandable nitinol anchors, proximal and distal, connected by a curvilinear ribbon and titanium crimp tubes, designed to plicate the tissue next to the MV annulus during the deployment process. The device is advanced in the CS until the distal anchor approaches the anterior commissure of the MV, where it will be unsheathed and locked. The delivery catheter is gently pulled to apply tension on the system and reduce the FMR. The proximal anchor is

positioned near the CS ostium and, after coronary angiography confirming uncompromised flow in the circumflex artery, the second anchor is deployed and locked. If the coronary angiography shows flow compromise in the left coronary artery, the device can be recaptured and repositioned.[27] Device dimensions and anchor location are chosen by direct measurement of the CS with a calibration catheter during venography. There are 37 possible combinations of anchors size and device lengths.[45] The device can be combined with a MitraClip procedure[45], and it does not preclude implantation of a CS lead for cardiac resynchronization.[46] It received CE mark approval in 2011 for the model XE2. **(Figure 14)**

The first-in-human feasibility study of the CARILLON® Mitral Contour System™ — AMADEUS (Mitral Annuloplasty Device European Union Study) trial— showed at 6-month follow-up favorable results with a significant reduction of MR and MA diameter, a trend towards reverse remodeling of the LV, preserved values of LVEF over time, and a significant improvement in exercise tolerance and quality of life.[47] The TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trial[48] was a prospective, non-randomized, open-label, multicenter study using a slightly improved version of the device: the CARILLON XE2. Compared with baseline, patients had a significant and stable reduction of MA mediolateral diameter, MR quantitative parameters and LV diameter and volume, along with a significant and sustained improvement up to 24 months in NYHA functional class and 6-minute walking test (6MWT). However, there were several cases of device wire fracture, though without adverse events or clinical events. To reduce the risk of fracture, the device underwent further enhancement in the most recent version — the CARILLON mXE2 — which was tested in the TITAN II trial.[49] The CARILLON mXE2 was associated with improvements in clinical and echocardiographic parameters in patients with FMR, while successfully addressing the issue of anchor fracture[49]. The CARILLON mXE2 was used in the REDUCE FMR (NCT02325830, www.clinicaltrials.gov) multicenter, double-blind, randomized clinical trial where symptomatic patients with FMR were compared with a randomized control group which is medically managed according to HF guidelines, with an estimated enrolment of 400 subjects.[50]

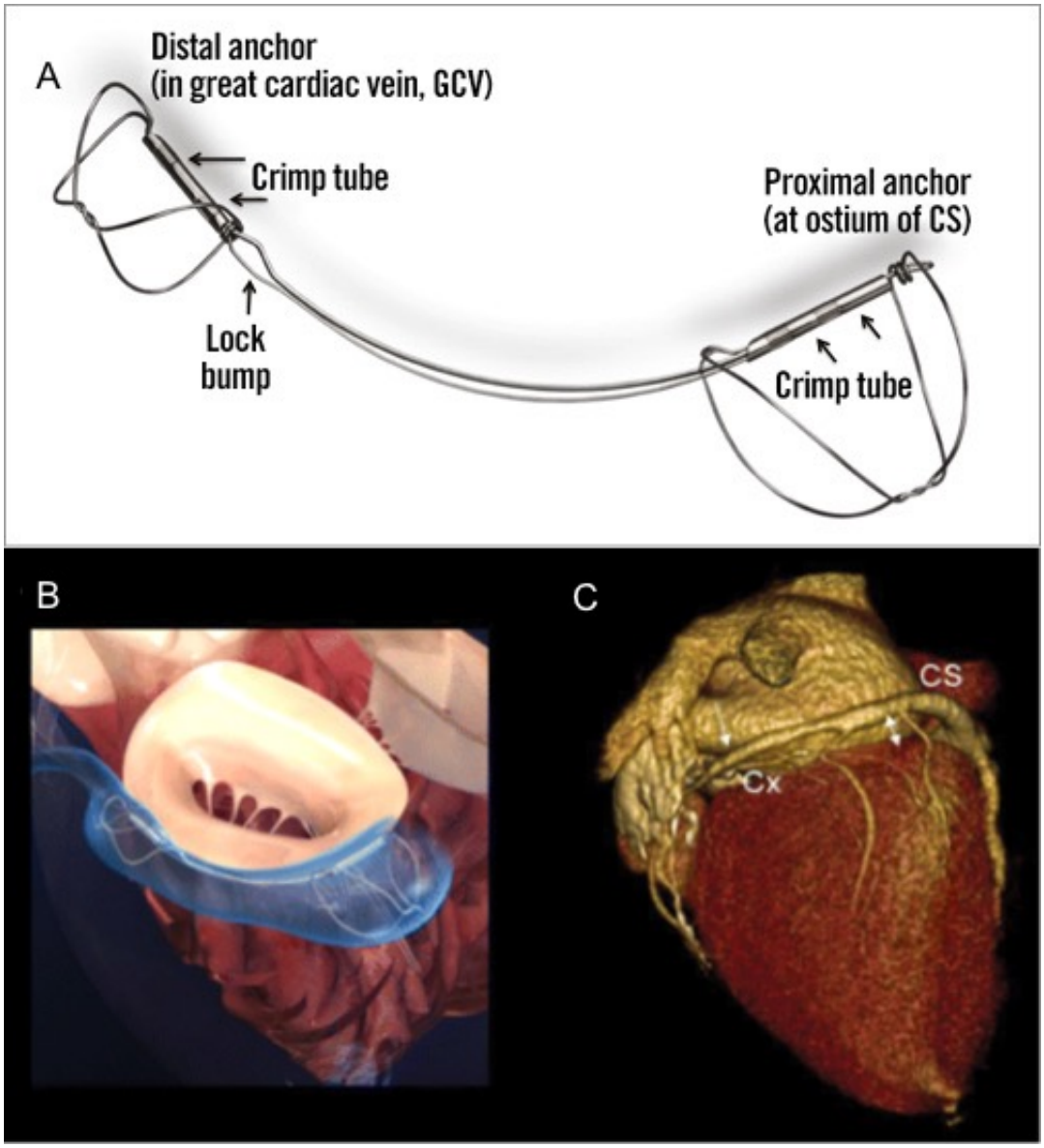

Figure 14 CARILLON® Mitral Contour System*. The system is designed to be implanted within the coronary sinus (CS) or the great cardiac vein (GCV) to reduce the cross-sectional area of the mitral annulus and subsequently to reduce the functional mitral regurgitation (A and B). The procedural feasibility and effectiveness of this device depend on the anatomical course of the coronary sinus in relation to the mitral annular plane and the circumflex artery (Cx). Multi-detector row computed tomography provides three-dimensional visualization of these spatial relationships and enables the relative distance between the CS and the mitral annular plane (double arrow) and the Cx (arrow) (C)*[51,52].

The ARTO™ system

The ARTO™ (MVRx Inc., Belmont, California) system is designed to increase leaflets coaptation in FMR by reducing the MA anteroposterior diameter by a connecting bridge between interatrial septum and CS. It can be considered part of the annuloplasty techniques, but it does not share a common approach, so we decided to describe it apart from the annuloplasty devices. Using

12-F sheaths, two magnetic catheters are introduced in the right internal jugular vein and right femoral vein, respectively. The first catheter is then placed in the CS and the latter in the LA, after the TS puncture. The two magnetic tips are linked posteriorly, in the LA, behind the posterior MV leaflet. A small puncturing wire is advanced from the CS into the LA to create a continuous loop wire from the right internal jugular vein to the ipsilateral femoral vein. A CS anchor is placed and connected to an atrial septal anchor by an adjustable suture, so the anteroposterior diameter of the MA can be shortened until significant reduction in MR is obtained under TEE guidance. The suture is finally locked and the delivery system retrieved.[53] **(Figure 15)**

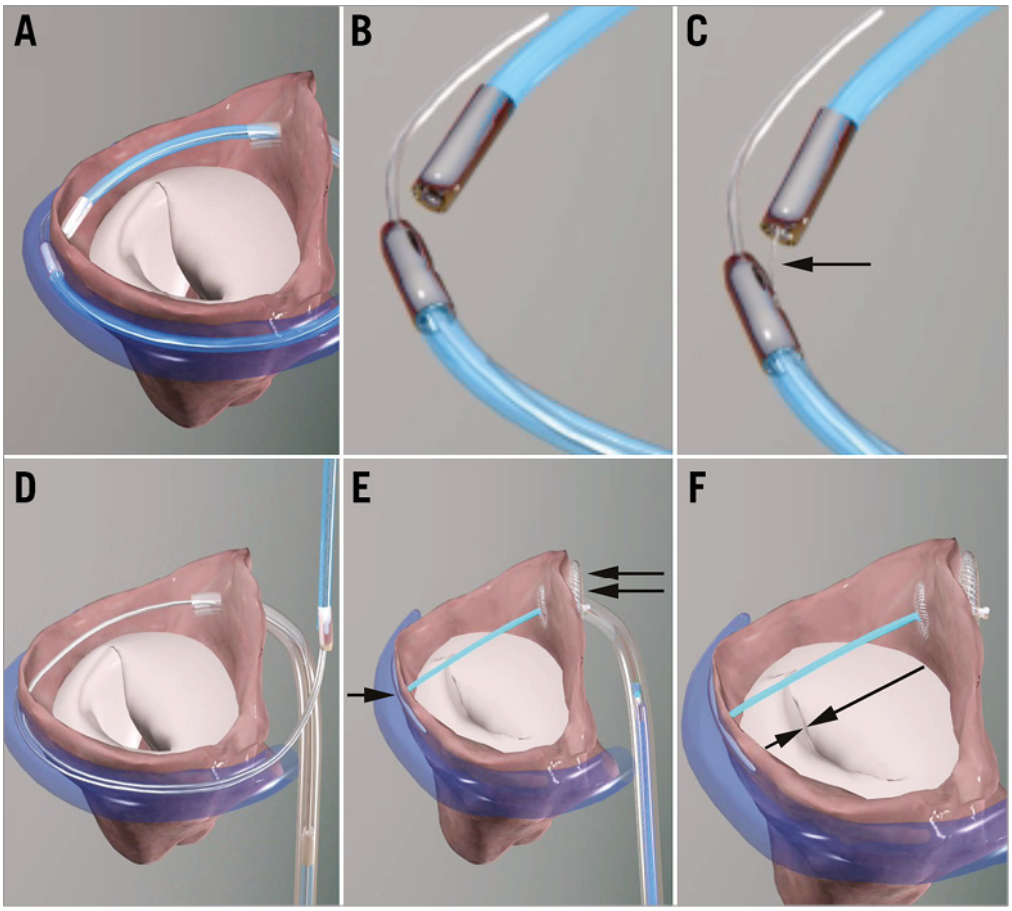

Figure 15 The Arto System implantation procedure*. A) Great cardiac vein (GCV) and left atrial (LA) MagneCaths in position and magnetically linked behind the P2 segment of the posterior mitral leaflet. B) Close-up of magnetically linked LA and GCV MagneCaths. Each magnetic catheter has a specific shape and lumen to direct and receive the crossing wire. C) The crossing wire (arrow) is pushed from the GCV into the LA MagneCath. The MagneCaths are aligned to direct the wire safely from the GCV to the LA through the atrial wall. D) After using an exchange catheter, the loop guidewire is placed across left atrium. This guidewire directs the placement of the GCV anchor (T-bar) and septal anchor. E) The MVRx System in place before tensioning. T-bar, single arrow; septal anchor, double arrow. F) Tensioning of the bridge results in precise shortening of the mitral annulus anteroposterior diameter (arrows) and reduction of FMR; once the final position is obtained, the suture is cut and secured with a suture lock.* [54].

The MAVERIC (Mitral Valve Repair Clinical Trial; NCT02302872, www.clinicaltrials.gov) is an ongoing first-in-human, multi-center, observational study, enrolling patients with MR grade ≥2 and HF of any etiology (NYHA functional Class II-IV) who could not undergo MV surgery.[53] To date, more than 45 patients have been enrolled and 11 of them reached 3-year follow-up. Technical success was obtained in all patients and at 30-day follow-up an improvement in MR grade, MA anteroposterior diameter, LV dimensions, and NYHA functional class was observed; no deaths, myocardial infarction or stroke were reported. At 2-year follow-up, there was a reduction of 64% in HF rehospitalization.[54] These improvements were sustained from 1 to 3-year follow-up.[55,56]

3) Chordal implantation

Among the different surgical strategies, the "respect rather than resect" approach with implantation of one or more artificial chords represents an alternative for patients with primary MR.[57] Three mini-invasive devices have been developed to replicate chordal implantation in a beating heart without cardiopulmonary bypass: the NeoChord DS100 Delivery System (NeoChord, Inc., Eden Praire, MN, USA) and MitraFlex™ (TransCardiac Therapeutics, Atlanta, GA, USA) intended for a transapical (TA) approach and the Babic device by a TS route. Among them, only the NeoChord DS100 Delivery System (NeoChord, Inc., Eden Praire, MN, USA) is CE marked for the treatment of primary MR regardless of the risk profile of the patient. Artificial cords have never been used in patients with FMR.

Transcatheter mitral valve implantation

Important challenges needed to be overcome for the development of the prostheses and make feasible the delivery. The MV apparatus anatomy is extremely complex leading to significant delays in the implementation of this transcatheter strategy in the clinical practice.[58] First, the MA presents

close anatomic relationship with the left ventricle outflow tract (LVOT), aortic valve structures, CS and circumflex artery which imply a potential risk of compression and damage during or after valve replacement.[58] Second, the MA shows asymmetrically saddle-shape with large dimensions which translates into large prostheses and delivery systems.[58] Third, the MA is a dynamic structure which does not complies well with rigid devices.[58]

The implantation of a MV prosthesis in a native valve, as in the case of FMR, is additionally demanding since the landing zone is usually consisting of a dilated MA, with no or minimal calcification. Compared with transcatheter aortic valve implantation, the younger age of patients with MR, the broadly heterogeneous pattern of MV disease, and the absence of a validated transcatheter treatment for the frequently associated significant tricuspid regurgitation produced additional issues in the development process of the prostheses. To the best of our knowledge, there are at least 30 TMVR systems under development and they actually represent only the devices that have reached the feasibility study in humans stage.

TIARA™ valve system

The Tiara valve (Neovasc Inc., Richmond, British Columbia, Canada) consists of a nitinol self-expanding frame and three leaflets of bovine pericardium. It is D-shaped and characterized by an atrial skirt and a ventricular anchoring system for the trigones and the posterior MA that can capture the native anterior and posterior leaflets.[59] Prosthesis size ranges from 30 to 45 mm. Implantation is performed through TA approach, with a 32-F delivery system, by TEE and fluoroscopy guidance. When the device is advanced in the LA, the valve is partially unsheathed to allow the orientation and alignment of the flat part of the D-shaped prosthesis towards the aorta. Next, the device is pulled back to reach the atrio-ventricular groove and subsequently unsheathed to release the anchoring system and fully deploy the valve.[60] **(Figure 16)**

After preclinical evaluation,[6] a total of 56 patients with severe FMR and primary MR and high surgical risk have been successfully treated with Tiara implantation to date[61]: 40 patients were

enrolled in the TIARA-I feasibility clinical study (NCT02276547, www.clinicaltrials.gov) and 16 patients were enrolled in the TIARA II CE Mark study (NCT03039855, www.clinicaltrials.gov). Paravalvular leaks were reported as absent/trace/mild in 100% of the cases. Four deaths were reported 30 days after implantation.[59,60,62]

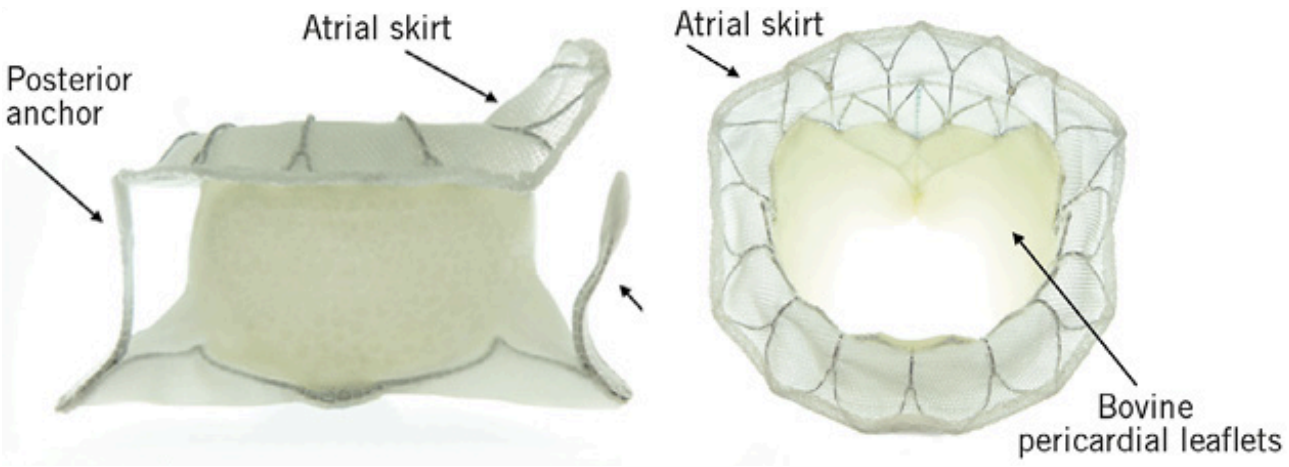

Figure 16 TIARA™ valve system[63]

FORTIS valve system

The FORTIS valve (Edwards Lifesciences, Irvine, CA, USA) is made of a self-expandable nitinol frame, three symmetric bovine leaflets, an atrial flange, and two opposing paddles that capture the native leaflets and secure them. **(Figure 17)** The only available size is 29 mm and the implantation is performed through apical access via a 42-F delivery system, under TEE and fluoroscopy guidance. After the valve is advanced in the mid-LV cavity, the paddles are partially unsheathed and oriented to engage the A2-P2 scallops, and then are fully exposed. The device is later advanced in the LA and the atrial flange is released first, followed by the valve.[64,65]

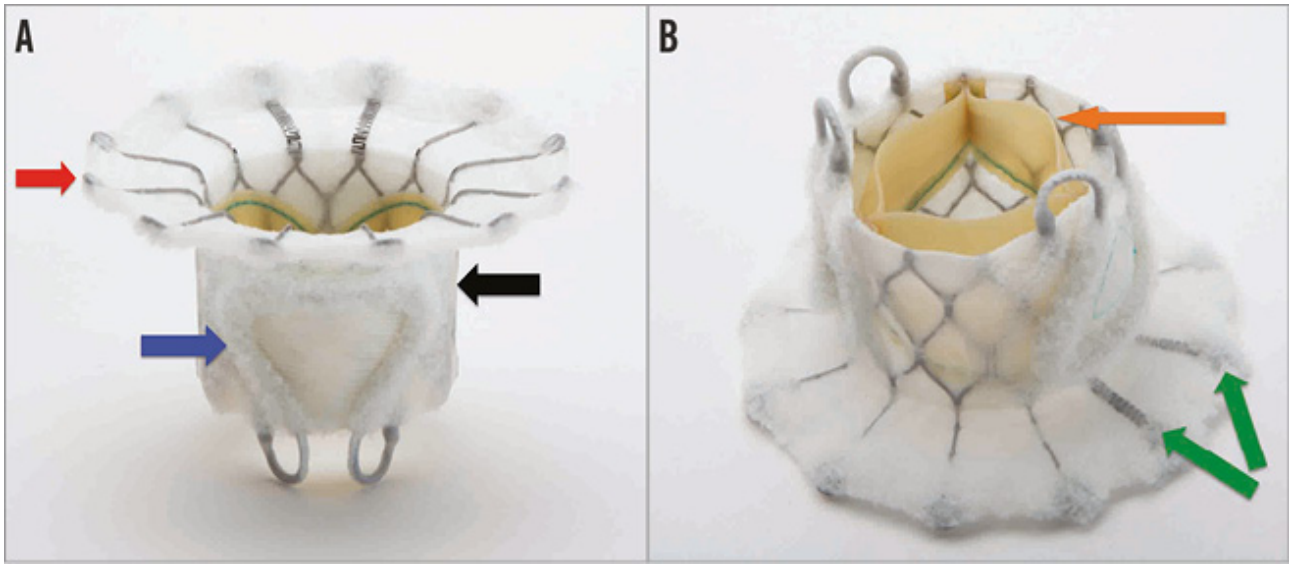

Figure 17 FORTIS transcatheter mitral valve*. A) Side profile of the FORTIS valve highlighting the atrial flange (red arrow), body of the FORTIS valve (black arrow) and one of the two paddles (blue arrow). B) Side profile of the FORTIS valve highlighting the bovine pericardial leaflets (orange arrow) and the flexible struts (green arrows), which align with the A2 segment of the mitral valve.*[65]

Bapat et al.[66] reported the results of 13 patients, among the 20 that received Fortis valve for compassionate use or in the context of the feasibility study. All the patients fulfilled the anatomical criteria for the only available size (29 mm).[65] Procedural success was obtained in 76.8% of patients (10/13) with 2 conversions to conventional heart surgery. In-hospital and 30-day mortality were 30.8% (4/13) and 38.5% (5/13) respectively. The echocardiographic assessment confirmed the good function of the prosthesis at discharge.[66] Two patients died during the 2-year follow-up due to terminal HF, leading to an all-cause mortality rate of 54%. Sustained MR reduction was documented at 2-year follow-up.[64] In May 2015, Edwards Lifesciences temporally paused the Fortis valve program for a thrombotic issue. In August 2015, the company acquired the CardiaAQ (Valve Technologies Inc., Irvine, CA, USA).

CardiaAQ™ valve system

The CardiAQ valve system (Edwards Lifesciences, Irvine, CA, USA) is composed by a self-expandable nitinol frame with three bovine tissue leaflets, designed for both TA and TS access, by using two different delivery systems (33-F). The device has an inflow and an annular part (30 and 40

mm diameters respectively), designed for MA dimensions ranging between 36 and 39.5 mm. The valve is symmetric, characteristic that overcome orientation issues, and equipped with two sets of opposing anchors: the LV anchors, covered by polyurethane foams to reduce tissue injury and designed to engage the leaflets and the sub-valvular apparatus, and the LA anchors which ensures axial stability. The frame is covered by a polyester fabric skirt to reduce the possible leaks.[67,68] **(Figure 18)** Regardless of the access route, before navigation of delivery catheter in the LV, the wire pathway is checked for impingement of the mitral sub-valvular apparatus (Copenhagen maneuver) using a 46 mm Reliant balloon catheter (Medtronic, Mineapolis, MN, USA). When CardiAQ is centrally positioned at the level of the MV plane, LV anchors are flipped and the device is progressively expanded to capture both leaflets. Once MV leaflets catching is confirmed by TEE, the LA anchors are exposed and the device is completely deployed in a supra-annular/intra-annular position to avoid LVOT obstruction.[67,68]

Early results from compassionate implantation of the 2nd generation of the CardiAQ (three TA[69] and one TS implantation[67]) demonstrated that both approaches are feasible and effective. The early feasibility study using TS delivery system is ongoing in the United States (NCT02718001, www.clicaltrials.gov) and it is estimated to enroll a total of 30 patients with MR grade ≥2 and high risk for conventional surgery.

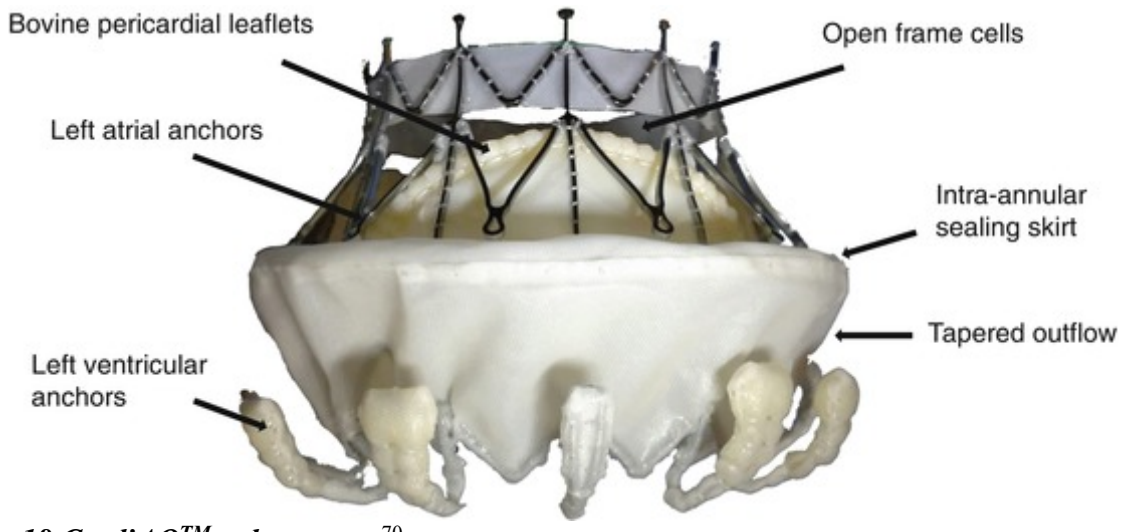

Figure 18 CardiAQ™ valve system[70]

TENDYNE valve system

The Tendyne valve (Abbott Vascular, Abbott Park, IL, USA) is designed for both FMR and primary MR and consists of two self-expandable nitinol frames – a D-shaped outer frame and a circular inner frame - with three porcine pericardium leaflets and an epicardial pad.[71] **(Figure 19)** Valve implantation is performed under fluoroscopy and TEE guidance using a TA delivery sheath (34-F) that is inserted perpendicularly to the MV plane. The wire path is checked with a balloon-tipped catheter. After introducing the prosthesis in the LA and having partially deployed it, the orientation of the frame is checked so that the flat part of the D-shaped outer frame is placed against the mitro-aortic continuity. The device is therefore retracted to land in the MV groove for the complete deployement. The last step is the insertion of the epicardial pad and the adjustment of the tether tension.[71,72]

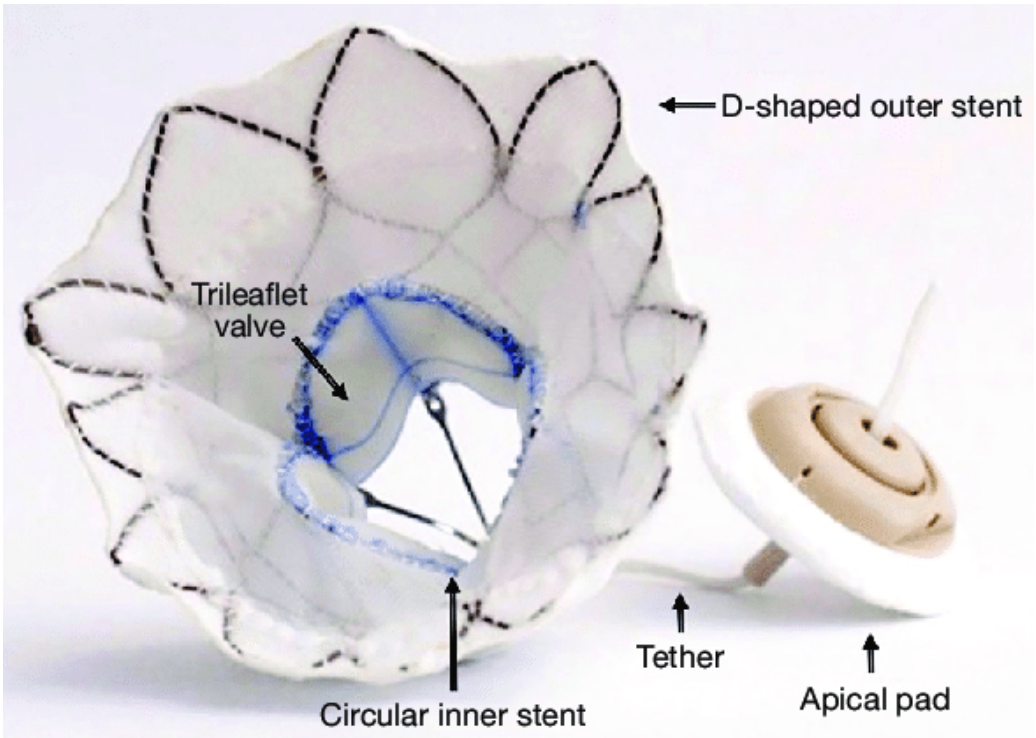

Figure 19 TENDYNE Valve System[73]

In 2014 Lutter et al.[8] reported the results of an acute human study, in which prostheses were implanted and observed for 2 hours in 2 patients with primary MR before conventional MV surgical replacement, that showed the feasibility of the TA approach with reduction of the MR grade. The

first-in-human experience with three compassionate implantations (two FMR) confirmed the feasibility and the acute success of the procedure.[72] The ongoing global feasibility trial (NCT02321514, www.clinicaltrials.gov) is enrolling high surgical risk patients with severe FMR and primary MR who are not suitable for conventional MV repair or replacement.[74,75] A total of 350 subjects at more than 40 centers is planned to be enrolled in the study. Muller et al. reported the overall experience in 30 patients (23 with secondary MR) until March 2016, with a successful implantation in 28 (93.3%) of them. There were no acute deaths, strokes or myocardial infarctions. At 30-day follow-up, MR was absent in 26 patients and trivial in one case. Significant LV remodelling was observed in all cases.

INTREPID valve system

The Intrepid TMVR system (Medtronic, Minneapolis, MN, USA) has two interconnected self-expandable nitinol stents - a circular 27-mm inner stent and an outer fixation ring with three available sizes of 43, 46 and 50 mm - with three bovine pericardial tissue leaflets and a flexible brim. **(Figure 20)** The outer ring is designed to conform the MV dynamic anatomy without distortion of the inner stent and the leaflets and is intended to be fixed to the MA by the radial force. The procedure is performed through TA approach, under TEE and fluoroscopy guidance. Once delivery catheter is coaxial with the MV and the system is advanced into the LA, the valve is oriented to align the support arms to the A2-P2 scallops and then expanded until the brim is completely deployed. The catheter is subsequently retracted in the atrio-ventricular groove and the fixation ring is also expanded until the valve is completely released. The Intrepid TMVR system does not require rotational alignment or capturing of the MV leaflets.[76]

The Twelve Intrepid TMVR Pilot Study (Evaluation of the Safety and Performance of the Twelve Intrepid Transcatheter Mitral Valve Replacement System in High Risk Patients with Severe,

Symptomatic Mitral Regurgitation; NCT02322840, www.clinicaltrials.gov), including 50 patients with severe MR (84% with FMR) and high risk for conservative MV surgery, showed successful implantation in 48 cases. One patient had bleeding during the apical access and there was one failure of implantation due to sizing miscalculation and mispositioning of the valve. At 30-day follow-up, 7 deaths were reported and 5 patients needed reoperation due to access site bleeding. However, significant reduction in MR was observed in all alive patients and mild or no symptoms were reported in 79% of cases.[7]

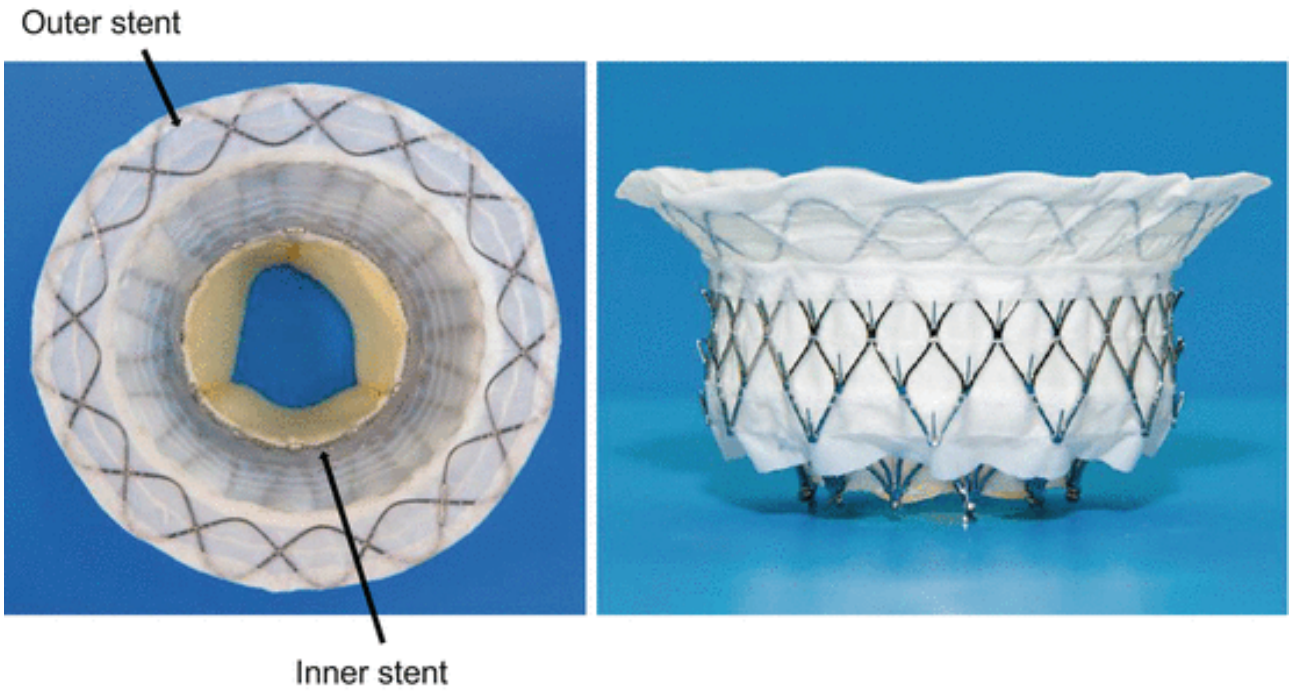

Figure 20 INTREPID valve[70]

The APOLLO trial (Transcatheter Mitral Valve Replacement with the Medtronic Intrepid TMVR System in Patients with Severe Symptomatic Mitral Regurgitation Study; NCT03242642, www.clinicaltrials.gov) will consists of a cohort of about 650 patients amenable to conventional open-heart MV replacement, randomly assigned to either Intrepid or surgery, and a single arm cohort of about 550 patients with high risk for conventional MV surgery undergoing TMVR procedure with the Intrepid TMVR system.

HighLife valve system

The HighLife mitral valve (HighLife Inc., Paris, France) system has two components, a 31-mm sub-annular implant and a nitinol self-extendable frame with three leaflets of bovine pericardium, together creating a "valve-in-ring" implantation.[77] The prosthesis is available only in a single size. Its shape has a preformed groove in the annular region so that it fits the sub-annular locking component.[78] The prosthesis can be deployed both through TA and TS access, while the locking component is implanted in the sub-valvular apparatus by retrograde approach via femoral artery. When the valve delivery catheter crosses the native MV and sub-annular implant, the valve is partially deployed in the LV and subsequently moved to reach MV ring. The final step is the complete deployment in the LA.[78] **(Figure 21)**

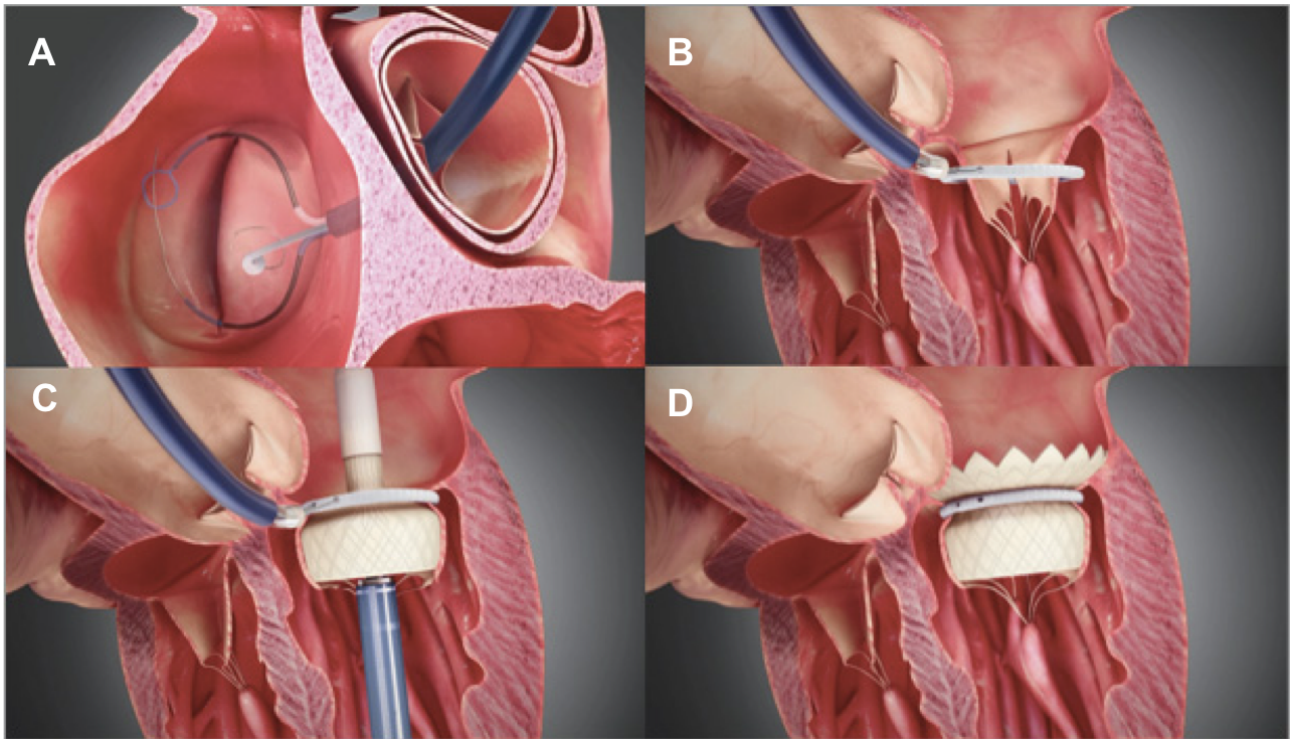

Figure 21 HIGHLIFE valve implantation. *(A-B) The catheter for the loop placement (LPC) is advanced using a retrograde approach through the aortic valve. A guidewire loop is placed and both ends externalized. The delivery and closure of the sub-annular implant (SAI) are carried out with a dedicated 18 Fr delivery catheter (SDC) hosting the SAI and the two ends of the previously placed guidewire loop. (C) The TMV delivery catheter is inserted through either the transapical (shown above) or the transatrial access. The outflow end of the TMV is deployed distal from the SAI and the SAI positioned close to the native annulus. (D) Then, the inflow end of the TMV is deployed by the delivery catheter.*[78]

A preclinical study showed the safety of the procedure and the histological examination from chronic models revealed tissue growth around the sub-annular ring with subsequent stabilization of the implant and leak prevention.[78] The first-in-human experience with two compassionate implantations was reported in August 2017. Both valves were implanted through apical access and no intraoperative complications were reported. The echocardiographic assessment showed excellent prosthetic valve function with only mild intra-prosthetic regurgitation. One patient survived and the 5-month follow-up showed excellent prosthesis performance. The second patient died after 4 days, despite a technically successful procedure, probably because of LV overload. A multi-center feasibility study is ongoing (NCT02974881, www.clinicaltrials.gov) and recruiting patients with severe MR, unsuitable for surgical treatment.

AccuFit valve system

The AccuFit system (Sino Medical Sciences Technology Inc., Tianjin, China) is composed of a self-expandable nitinol frame with three bovine pericardial leaflets, equipped with a supra-annular fixation and mitral-clipping anchoring mechanism.[79] The frame is divided into an atrial and a ventricular flange and the annular support is composed of a row of anchoring clips to secure the native valve. The clipping area is covered with a skirt, which is in continuity with the atrial flange in order to avoid paravalvular leaks. **(Figure 22)** The initial reverse design of the leaflets, with a central diastolic opposition and a circumferential coaptation, was abandoned in favor of the current conventional prosthesis design.[79,80] Currently available size range is 30-42 mm, with 4 mm increments. Valve protrusion in the LV is less than 14 mm to avoid the LVOT interaction. Procedure is performed through TA approach, using a 38-F delivery catheter, under TEE and fluoroscopy guidance. The delivery requires 4 steps: (1) device unsheathing and localization at the MV annulus plane; (2) ventricular flange advancing to entrap MV leaflets; (3) atrial flange release to clipping annulus and (4) complete deployment of the prosthesis.[81] A preclinical study demonstrated the safety

of the procedure, with minimal paravalvular leakage and LVOT obstruction.[80,81] A D-shaped atrial flange is under evaluation.[81]

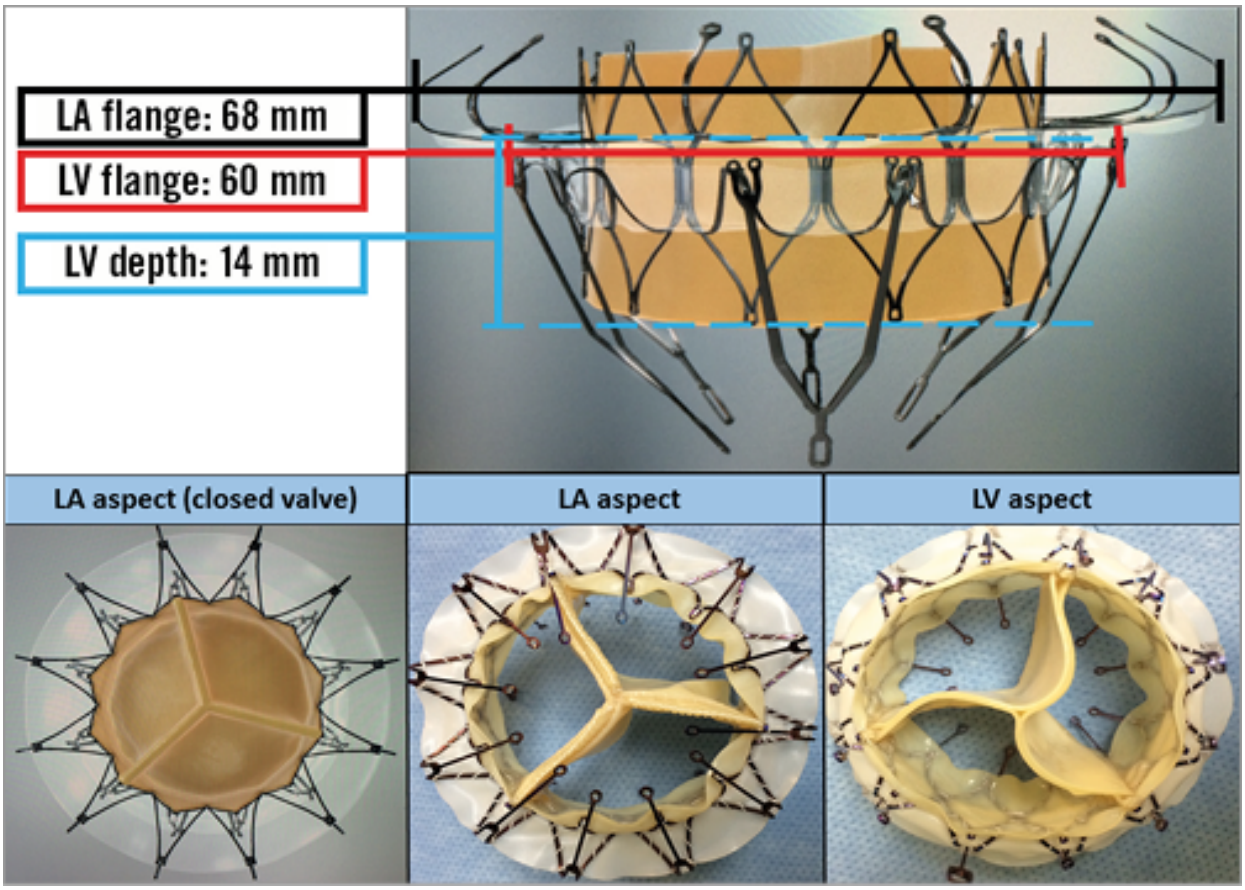

Figure 22 The AccuFit™ TMVR prosthesis*. The atrial aspect (left, lower) and the ventricular aspect (right, lower) displaying the reverse leaflet design*[80]

Caisson valve system

The Caisson TMVR system (LivaNova PLC, London, England) is a two-component device, consisting of an anchor and a three-leaflet porcine pericardial valve. The anchor is a D-shaped self-expanding nitinol structure that serves as foundation for the valve and grips the native MV. **(Figure 23)** The prothesis is delivered through transfemoral approach, using a 31-F delivery system.[82] The first-in-human implants were successfully performed in the United States in 2016.[83] An ongoing feasibility study - the PRELUDE (Percutaneous mitral valve replacement evaluation utilizing the investigational device exemption early feasibility study; NCT02768402, www.clinicaltrials.gov),

with an estimated final enrolment of 20 subjects, is currently recruiting patients, but no data is available so far.

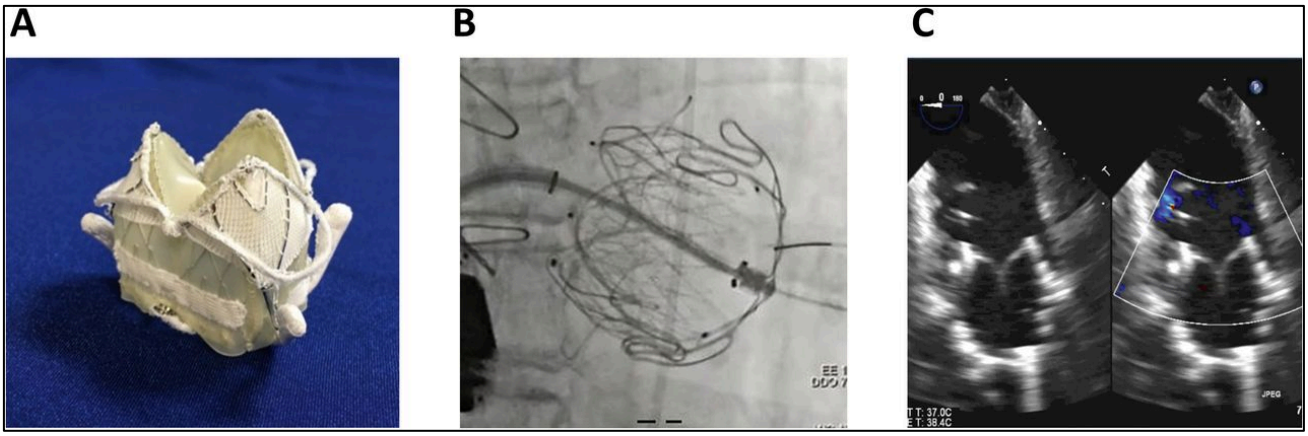

Figure 23 Caisson Valve*. (A) Valve prosthesis. (B) Fluoroscopy. (C) Two-dimensional transesophageal echocardiography*.[84]

MValve system

The MValve docking device (Boston Scientific Corporation, Marlborough, MA, US) is not a valve *per se*, but a support platform that can be anchored within the mitral annulus, enabling the implantation of an approved transcatheter valve prosthesis. The first-in-human experience was performed in September 2015, in a patient with rheumatic valve disease, with no major periprocedural complications.[85] The feasibility study (NCT02719912, www.clinicaltrials.gov) will evaluate the MValve device in conjunction with the LOTUS system (Boston Scientific Corporation, Marlborough, MA, US) in high risk patients, with severe primary MR and FMR. The company is currently working on the design of the next generation of MValve and the recruitment status is unknown so far.

Current challenges of transchateter mitral valve replacement

Although epidemiological data underline the unmet clinical need of optimal therapeutic approach for secondary MR, it has been reported an elevated screening failure among patients candidate to new transcatheter intervention mainly due to clinical and anatomical factors (e.g. >70% in the Intrepid Global Pilot Study).[86] Moreover, several complications associated with TMVR have

been described across the feasibility studies. Smaller-size delivery catheters with very high flexibility and prostheses with favourable profile are required to reach the MV through a TS access and actually most of the available systems do not satisfy such requirements and need a mandatory more invasive TA approach. The complex three-dimensional anatomy and the high-pressure gradient generated by the LV during systole contribute to the frequent occurrence of paravalvular leakage and several technical improvements were made during recent years to overcome these issues. Considering the significant geometrical LV abnormalities in patients with FMR, the development of a prosthesis with optimal adherence to the MA is extremely challenging. In the FMR subset, the MA usually has low-grade or no calcifications making the anchoring of the valve more unstable. The radial stiffness of the prosthesis needs to be carefully optimized to get enough strength to avoid the fracture of the frame over time and enough flexibility to avoid the perforation of adjacent structures without increasing the risk of displacement or embolization.[87] LVOT obstruction has been described after surgical MV procedures[88], valve-in-valve or valve-in-ring[89,90] interventions and TMVR shares this potential complication too. TMVR systems that are not designed to capture the native MV leaflets are more prone to bulking into the LVOT.[91] Multiple risk factors should be evaluated when assessing the risk of LVOT obstruction with TMVR procedure: (1) an acute aorto-mitral annular angle (the angle between the annular planes of the two valves); (2) septal hypertrophy in the basal segment; (3) valve protrusion in the LV.[92] **(Figure 24)** Iatrogenic atrial septal defect is a common complication after TS approach and it can be associated with right-sided heart enlargement, worsening of the tricuspid regurgitation and higher re-hospitalization rates for HF. The further improvements in available technology or the development of novel systems will help in overcoming most of the issues identified during and following TMVR procedure.

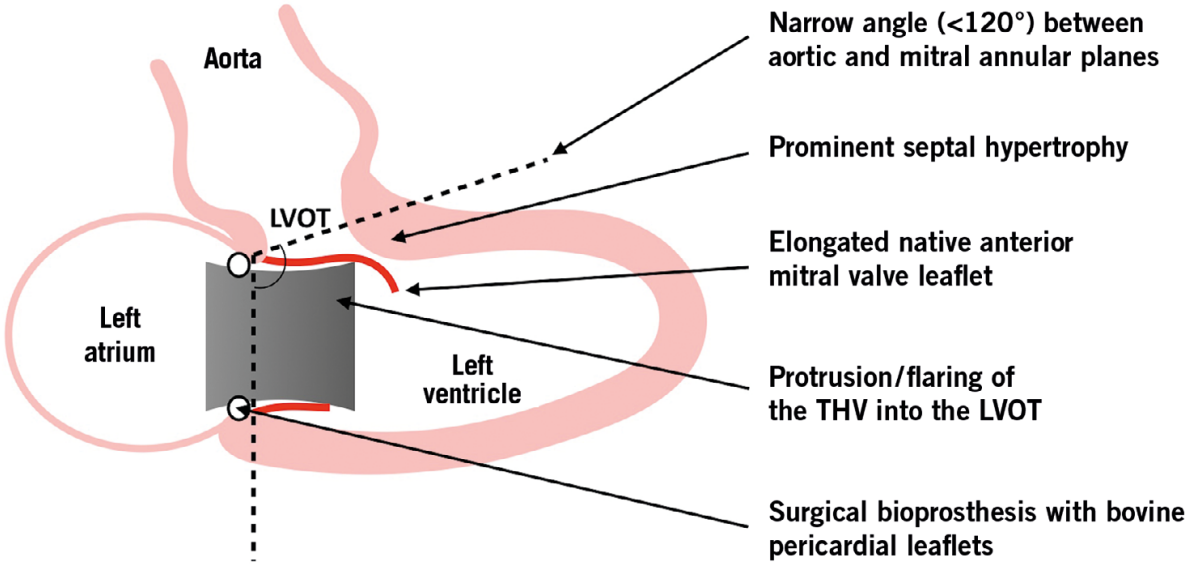

Figure 24 Risk factors for LVOT obstruction during a valve-in-valve transcatheter mitral valve implantation. *THV: transcatheter heart valve*[90]

Experimental section

The research project consists of three sub-studies:

1) Preclinical study assessing the feasibility and early safety of a novel mitral valve self-expandable prosthesis

2) Evaluation of the prosthesis function by hemodynamic surrogate parameters and blood flow characteristics

3) Assessment of the mitral valve anatomy using three-dimensional echocardiography in patients with functional mitral valve regurgitation focusing on the anatomical implications for prosthesis-based transcatheter approach

1. Preclinical study assessing the feasibility and early safety of a novel mitral valve self-expandable prosthesis

The Epygon transcatheter mitral valve system (EPYGON s.a.s., Affluent Medical, Paris, France) is a self-expandable D-shape bioprosthesis consisting of an asymmetric stent and an advanced bovine pericardium tissue mono-leaflet. The asymmetric nitinol stent, with a shorter anterior part, was designed to minimize the risk of LVOT obstruction and at the same time reduce the interference with the LV wall. The advanced mono-leaflet replicates the physiological diastolic asymmetric flow inside the LV. The bioprosthesis has engagement bodies to maintain the traction over the papillary muscle preventing the development of LV sphericity after implantation and an anterior arm that captures and blocks the anterior leaflet preventing the LVOT obstruction after implantation. **(Figure 25-27)** Available sizes of the Epygon prosthesis are 34 mm, 36 mm and 38 mm according to the commissural diameter.

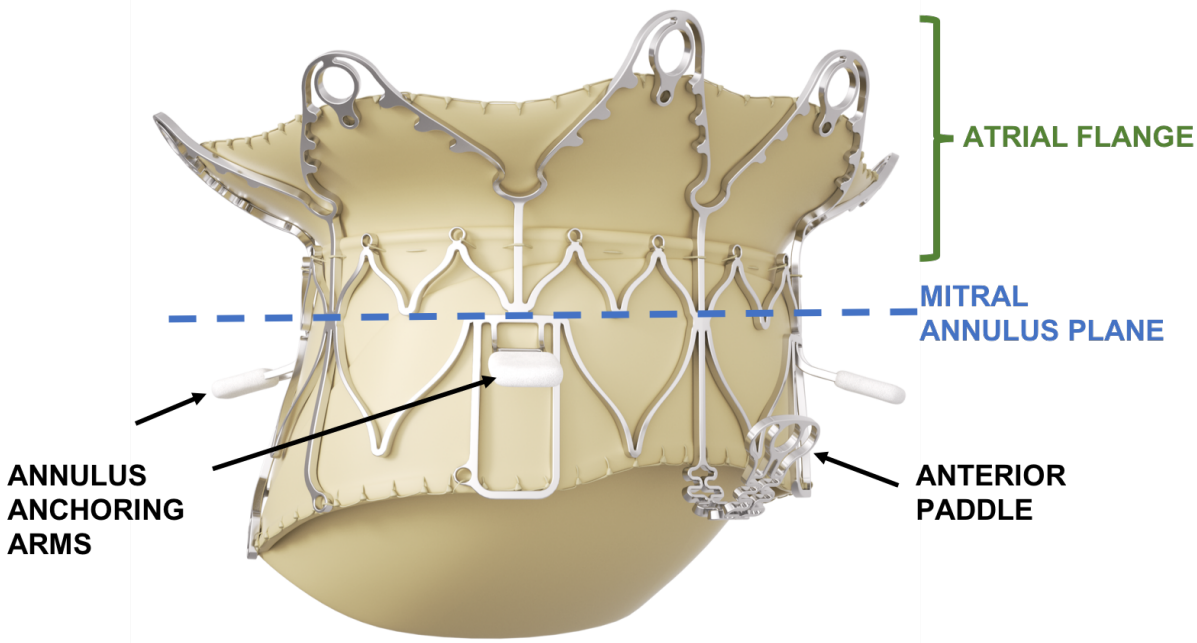

Figure 25 Epygon valve from lateral prospective

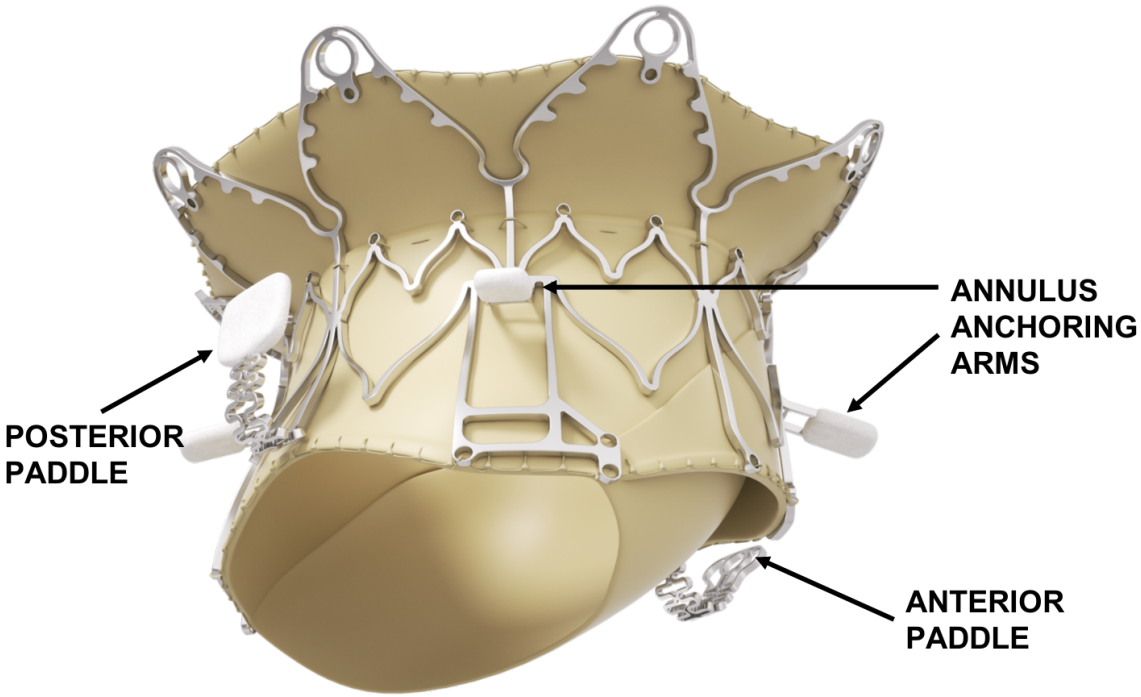

Figure 26 Epygon valve form posterior prospective

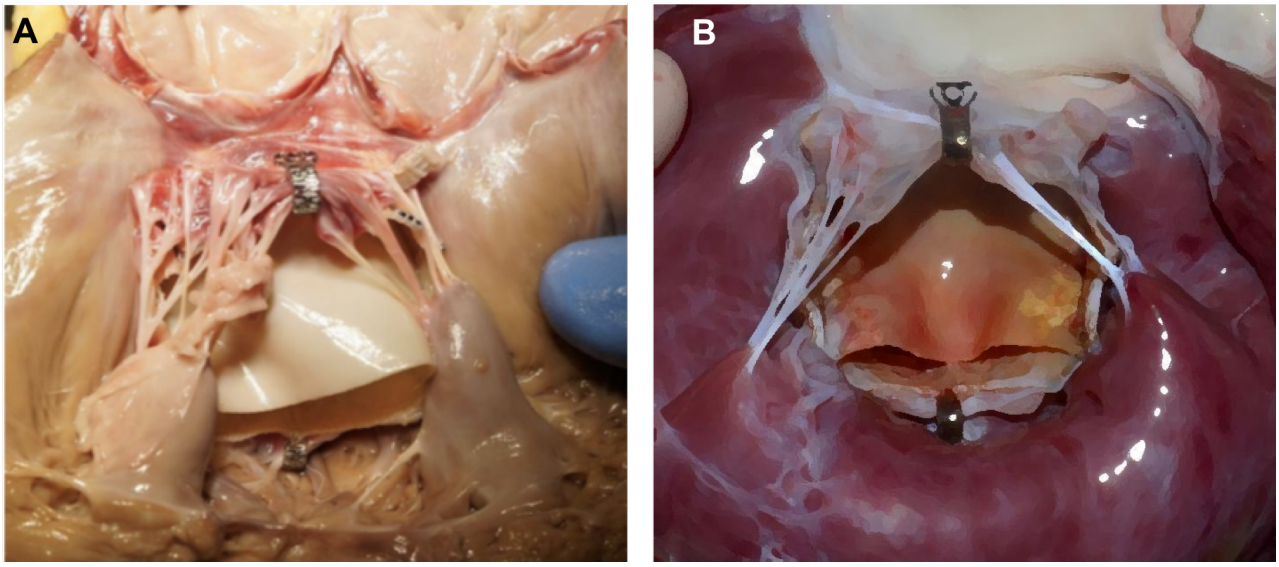

Figure 27 Ex-vivo and in-vivo implants of Epygon valve. *(A) Ex-vivo implant of the Epygon valve in a human heart. (B) In-vivo implant of the Epygon valve in a sheep heart at 5 months. In both figures, the anterior arm of the prosthesis captures the anterior leaflet of the mitral valve and maintains the traction over the papillary muscle preventing the future development of LV sphericity.*

The implantation of the Epygon valve is performed through TA approach, during echocardiographic and fluoroscopy guidance. TA implantation of the Epygon bioprosthesis in the preclinical stage of the development was performed by a multidisciplinary team including a cardiac surgeon, a veterinarian specialized in transcatheter procedures and an echocardiographer, through a small sub-xyphoid incision and under general anesthesia. When the device is advanced into the LA, the valve is partially unsheathed to allow the orientation and alignment of the flat part of the D-shaped prosthesis towards the aorta. Subsequently, the device is pulled back to reach the atrio-ventricular groove and then unsheathed to release the anchoring system and fully deploy the valve.

The preclinical development of the bioprosthesis was conducted at the Institut Mutualiste Montsouris Reserchers, Paris. From May 2015 to August 2018, the prototypes of the Epygon valve were implanted under echocardiography guidance in 112 small (50 ± 6 Kg) healthy sheep using both the Ta and TA access. The sheep were selected according to MA dimension at transthoracic echo (TTE, first 53 animals) and Multi Slice Computed Tomography (MSCT, last 59 animals). MSCT reconstruction allowed also the definition of the access site for the trans-apical approach. **(Figure 28)**

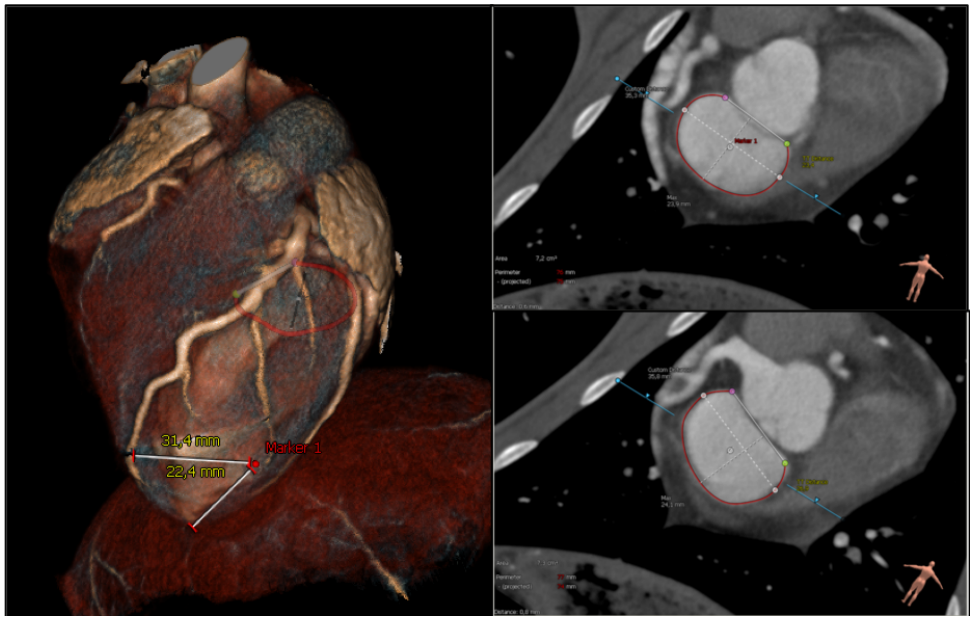

Figure 28 3D reconstruction of a sheep's heart. *Identification of site for puncture and mitral annulus measurement with a dedicated software (3Mensio, Pie Medical Imaging, the Netherlands).*

Before implantation, after thoracotomy, it was possible to acquire two- and three-dimensional transepicardial echo (TPE) from the left ventricular apex by using a transthoracic 4V probe or from the roof of the left atrium by using a transesophageal 6T probe. 3D data were post-processed to obtain MA dimensions. **(Figure 29, Table 2)**

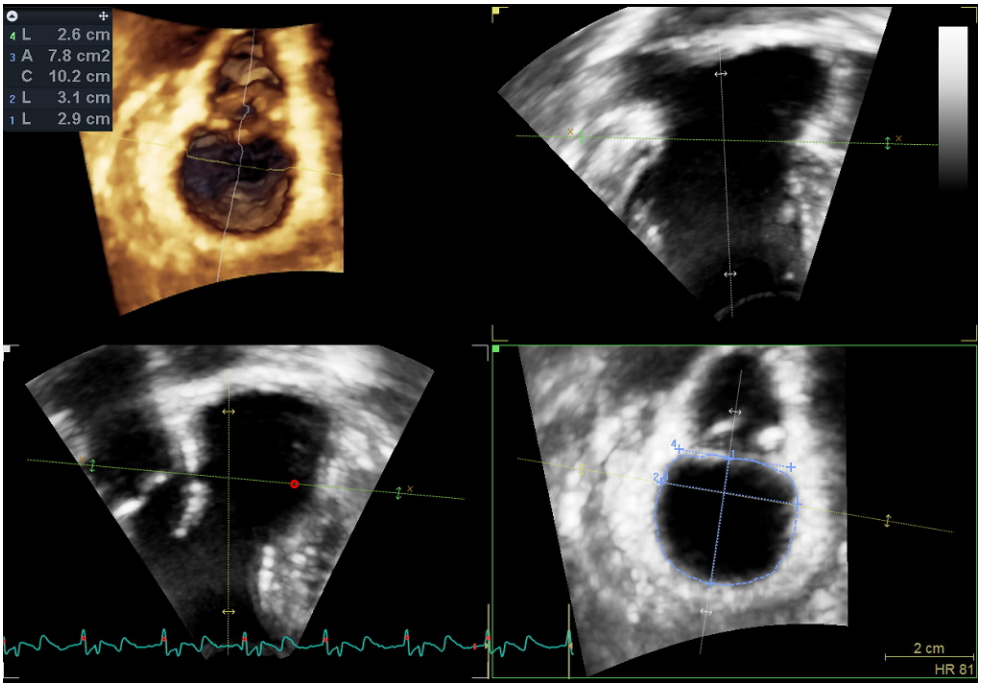

Figure 29 Mitral annulus study during the end-diastolic phase in a sheep model. *1: Antero-posterior diameter; 2: Anterolateral-posteromedial; 3: Area and perimeter of mitral annulus; 4: Intertrigonal distance.*

Table 2 Mitral annulus dimensions in mid-systole and early-diastole in 112 sheep.

	Diastole	Systole
Antero-posterior diameter (mm)	23 ± 2.6	20.9 ± 4
Commissural diameter (mm)	32.3 ± 2.6	31.3 ± 4.1
Perimeter (mm)	9.4 ± 0.8	9.1 ± 1.4
Area (cm^2)	6.4 ± 0.8	6 ± 1.1

During the first 10 sessions, both TA and Ta approach were tested. Later, TA implantation was selected as the best option and further improvements of both the prosthesis and the delivery catheter were made considering this access route. The first 20 implantations were guided only by angiography. TEE was also tested but it was abandoned due to absence of adequate acoustic window in the sheep model. Subsequently, intra-cardiac echo and a TEE probe in contact with pericardium to get advantage of its higher frequency, were combined and systematically applied to confirm the correct orientation and positioning of the valve. The stabilization of the TEE probe upon the roof of the left atrium did not interfere with delivery system **(Figure 30)** and generated "humanized" images. **(Figure 31)** In the last 54 sessions, the intra-cardiac echo and TEE-TPE contributed to the substantial improvement in the rates of successful implantation (>90%).

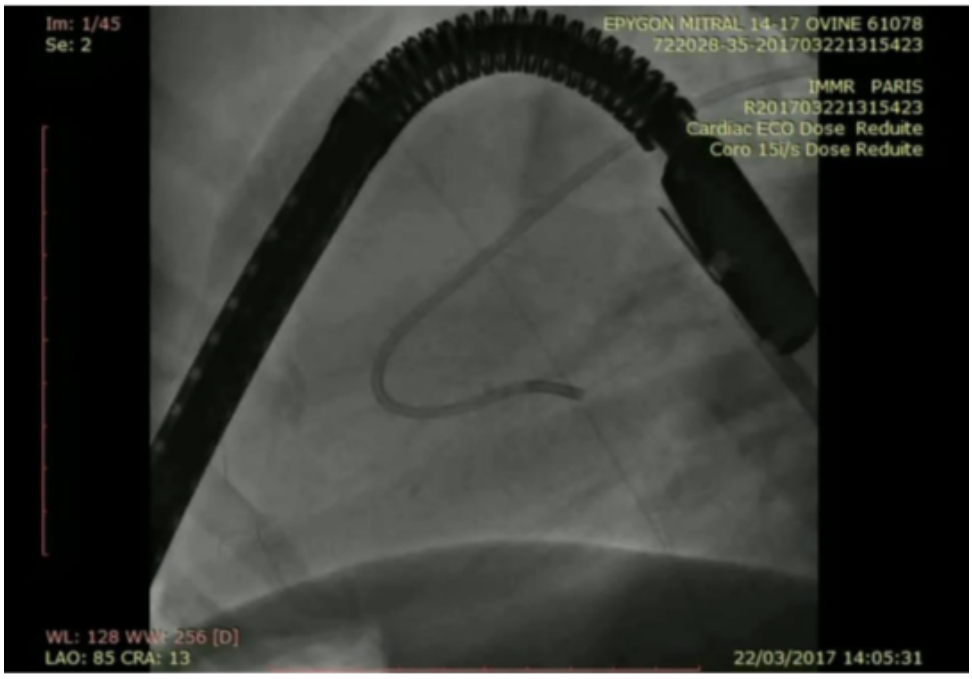

Figure 30 Fluoroscopy image of the transesophageal 6T echo probe placed upon the roof of the left atrium.

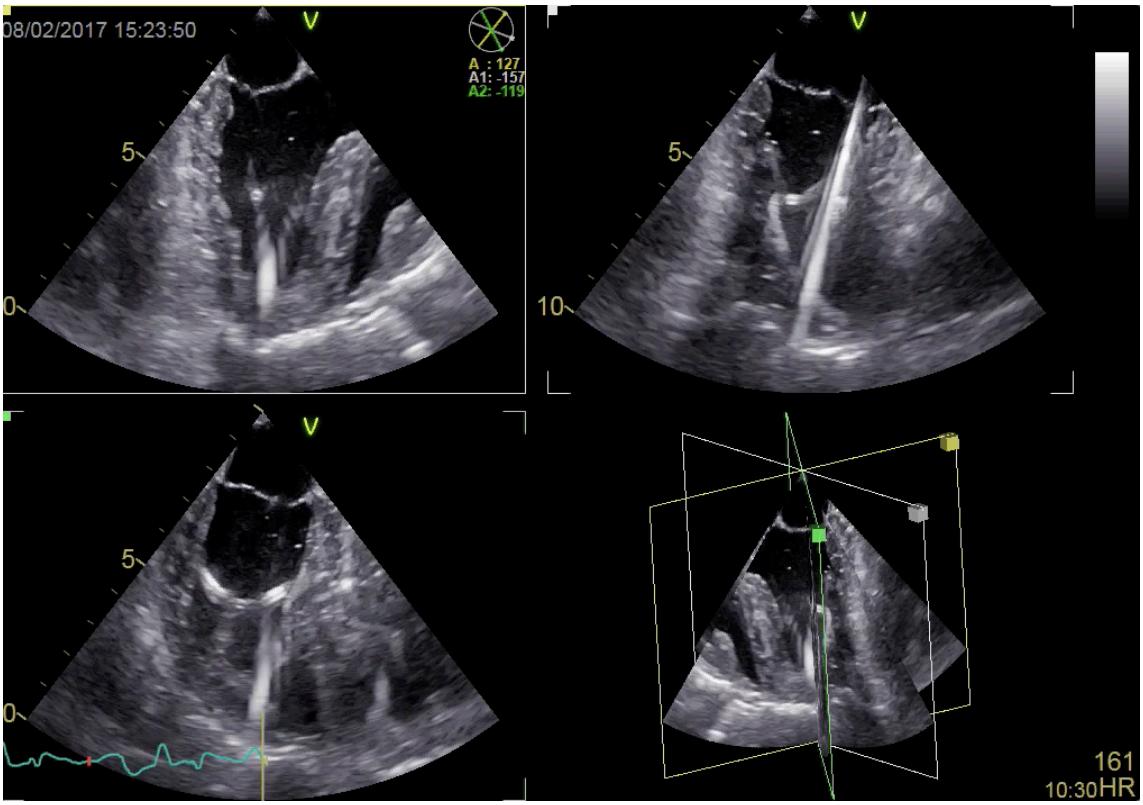

Figure 31 Humanized image obtained by transesophageal 6T echo probe placed upon the roof of the left atrium. *Multiplanar view during trans-apical puncture.*

2. Evaluation of the prosthesis function by hemodynamic surrogate parameters and blood flow characteristics

After implantation, the performance of the prosthesis was evaluated by using Doppler quantification, to assess trans-valvular gradient, intra- and peri-prosthetic leaks, and LVOT obstruction, and both 2D and 3D echocardiography, to analyze prosthesis orientation and functioning of anchoring system. In the vast majority of procedures there was none or trivial intra- (n=104, 93%) and peri-prosthesis leak (n=86, 77%) with good prosthesis function (mean gradient 4±3 mmHg); only one case of LVOT obstruction occurred due to prosthesis embolization during the first procedures. **(Table 3)**

Table 3 Doppler parameters after implantation of Epygon valve

		Mean ± DS/ N (%)
Mean gradient (mmHg)		4 ± 3
Periprosthetic leak		
	None	66 (59%)
	Trivial	20 (18%)
	Mild	24 (21%)
	Moderate	2 (2%)
	Severe	0
Intraprosthetic leak		
	None	96 (86%)
	Trivial	8 (7%)
	Mild	8 (7%)
	Moderate	0
	Severe	0
Left ventricular out flow tract obstruction		1

The impact of valve design on intraventricular flow dynamic was also studied using particle imaging velocimetry (EchoPIV). Two-dimensional harmonic imaging seeded with ultrasound microbubbles contrast agents was used. Swirling intracardiac flow motion is tracked by bubbles and then processed by dedicated software (Hyperflow). **(Figure 32)**

A preliminary analysis on 14 sheep seems to support the concept that the Epygon bioprosthesis respects the normal LV vortex properties of blood both in terms of dimension and orientation. Despite

vortex intensity decreased compared with the baseline, the anti-clockwise rotation was preserved (positive value of vortex intensity). **(Table 4, figure 32)**

Among the different LV energy properties, we found a significant 24.8% increase in energy dissipation (energy loss) after device implantation.

Flow force angle (FFA) reflects the dominant direction of blood flow momentum, that is 0° when the flow force is parallel with the LV long axis and 90° when the flow force is transversal; accordingly, a lower FFA would reflect a more efficient blood flow dynamic within the LV. After implantation, despite mean FFA significantly increased from 30° to 36°, the main axis of the flow roughly remained parallel to LV axis. **(Figure 32)** This finding may be partially explained by the presence of the suture stiches after trans-apical access closure that did not allow to place the probe in the same point before and after intervention with slight variation in the orientation of the LV long axis.

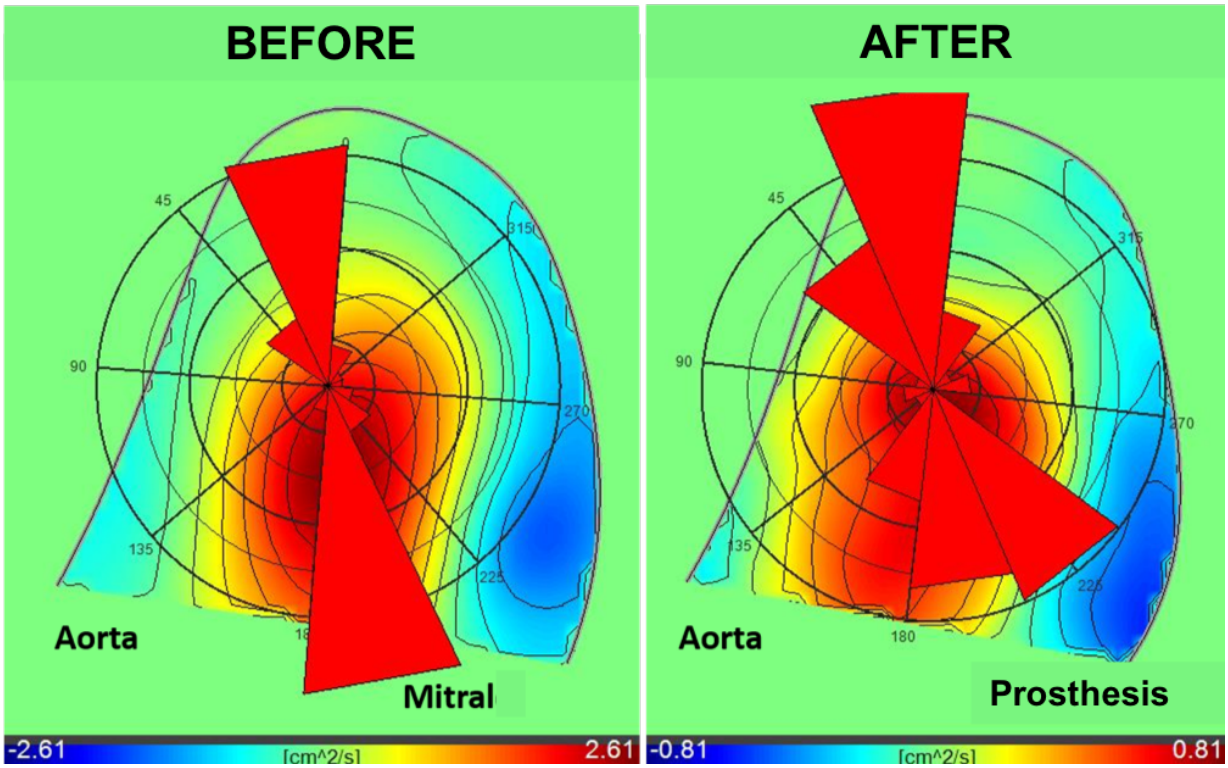

Figure 32 Example of the distribution of dominant flow force angle before and after implantation of the Epygon prosthesis. *The red triangles are histograms that illustrate both direction and amplitude of the left ventricular energy before (left panel) and after (right panel) prosthesis implantation. After the procedure (right panel), hemodynamic forces were parallel to the left ventricular axis.*

Table 4 Intra-cavity flow properties before and after implantation

	Before Implantation	**After Implantation**	**p**
Vortex Properties			
Area	0.21 ± 0.05	0.20 ± 0.07	0.067
Intensity	0.38 [0.32; 0.40]	0.29 [0.26; 0.35]	0.019
Depth	0.35 ± 0.09	0.28 ± 0.87	0.077
Length	0.59 ±0.16	0.49 ± 0.13	0.091
Energy Properties			
Energy dissipation	0.79 [0.65; 1.00]	1.14 [0.95; 1.37]	0.009
Vorticity fluctuation	0.80 ± 0.08	0.90 ± 0.03	0.001
Kinetic energy fluctuation	1.30 ± 0.27	1.66 ± 0.12	0.001
Shear stress fluctuation	-0.10 [-0.14; 0.17]	-0.38 [-0.22; 0.54)	0.110
Flow Force Properties			
Flow force angle (°)	30.2 ± 4.1	36.5 ± 5.1	0.002
Flow force dispersion angle (°)	43.4 [40.5; 53.7]	45.6 [43.2; 48.7]	0.778

Continuous variables distribution was tested by Kolmogorov-Smirnov test and accordingly displayed as mean ± standard deviation and compared by paired *t* test or median [25°; 75° percentile] and compared by Wilcoxon rank-signed test.

3. Assessment of the mitral valve anatomy using three-dimensional echocardiography in patients with functional mitral valve regurgitation focusing on the anatomical implications for prosthesis-based transcatheter approach

Mitral valve geometry quantification is of paramount importance for the success of TMVR, and transthoracic (TTE) three-dimensional echocardiography (3DE) represents a useful tool to select the patients with the highest likelihood of uncomplicated implant.[9] It has been previously reported that MV geometry may be different in ischemic and non-ischemic FMR. In patient with ischemic MR (IMR), regional wall motion abnormalities and left ventricular remodeling[10] are more often associated with mitral annulus (MA) asymmetric dilatation.[11] Conversely, in non-ischemic MR (nIMR) global LV remodeling leads to symmetric MA dilatation.[12] Yet, MV geometry in FMR has been mainly compared to organic MR, and only few small echocardiographic studies analyzed MV geometry differentiating between IMR and nIMR.[11-14] However, none of them provided MA geometry characterization framed to pre-procedural screening for TMVR.[9]

The aim of this study was to asses MV geometry in patients with FMR that would potentially benefit from TMVR, focusing on the comparison of MA geometry between IMR and nIMR patients in two key moments of the cardiac cycle —mid-systole and early-diastole.

Methods

Study population

Using the electronical database of the echocardiography laboratory of the department of Cardiac, Thoracic and Vascular Science of University of Padua, 94 patients with severe FMR and complete transthoracic echocardiography performed between November 2010 and March 2018, have been retrospectively selected. Inclusion criteria were: age > 18 years; severe FMR according to the

recommended multiparametric approach [93]; availability of good quality 3D data sets of both the left ventricle (LV) and the MV. We excluded patients with organic MR, mitral stenosis, aortic stenosis, more than moderate aortic regurgitation, or those with valve prostheses. Each patient was assigned to the IMR or nIMR subgroup according to his/her clinical history and the documentation of presence/absence of significant coronary artery diseases. The study was approved by the University of Padua Ethics Committee (protocol no. 70299).

Mitral valve analysis software package validation

Two sub-studies were carried on to validate the software package used to quantitate MV geometry (4D Auto MVQ, GE Vingmed Ultrasound AS, Horten, Norway). First, the same operator (P.A.) performed the quantitative analysis of the MV in a blinded fashion, and after a time interval of one month form each other, using the same TTE data sets and both the new and a previously validated[94,95] (4D MV Analysis; TomTec Imaging Systems, Unterschleissheim, Germany) software packages. Second, 3D TTE and transesophageal (TEE) echocardiographic MV data sets were analyzed using the same software package for MV quantitative analysis (4D Auto MVQ, GE Vingmed Ultrasound AS, Horten, Norway) by the same operator (P.A.) in a blinded fashion, after a time interval of one week.

Echocardiography and quantitative image analysis

All transthoracic examinations were performed using a commercially available Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 4V probe for 3DE acquisitions according to a standardized protocol. Image analysis was performed on a dedicated workstation equipped with a commercially available software package for offline analysis of 3D datasets (EchoPac 2.02). Quantification of LV volume and ejection fraction (LVEF) was performed using 4D Auto-LVQ software[96] (GE Vingmed Ultrasound AS, Horten, Norway). Left atrium (LA) maximum volume was measured using the biplane disk summation method, at LV end-systole.[97] MR severity and

conventional MV geometry parameters —antero-posterior (AP) and commissural (CC) diameters, tenting height and tenting area— were assessed according to current recommendations.[93] 3D MA analysis was performed on dedicated datasets by a single experienced observer (P.A.), using a new, commercially available, software package (4D Auto MVQ, GE Vingmed Ultrasound AS, Horten, Norway), in two moments of the cardiac cycle: early-diastole and mid-systole. Firstly, two time points were identified in the way that the selected frame of the analysis was midway among them. For mid-systolic analysis, the two time-points were early-systole (the frame after MV closure) and end-systole (the frame before MV begins to open). For early diastolic analysis, after identification of early-diastolic frame (first frame when MV start to open), the two time-points were placed 8 frames before and after the selected early-diastolic frame. The two orthogonal planes were adjusted to visualize the commissural and longitudinal view of MV (the longitudinal plane intersected the MV at the level of A2 and P2 scallops). For initialization, anatomic landmarks have to be added at the level of MA in the longitudinal view (posterior, P; anterior, A; leaflets coaptation point, Coap; and aortic valve, Ao) and commissural view (MA1 and MA2). The software package automatically created a 3D model of the MV in the selected frame which could eventually edited manually, if needed. **(Figure 33)** Quantitative parameters of the MV geometry, provided automatically, were: MA 3D area; MA 2D area (projected 2D area at the level of the best fit plane); MA perimeter; MA AP diameter, as the distance between the two landmarks A and P; MA anterolateral-posteromedial diameter (ALPM), as the longest diameter of MA perpendicular to AP diameter; sphericity index (as the ratio between AP and ALPM diameters); MA CC diameter, as the distance between the two commissure; MA inter-trigonal distance, measured between the two automatically identified trigons; MA height, as the distance between the lowest and the highest points of MA; the non-planimetry angle, that assesses the saddle shape of MA; mitral-aortic angle, as the angle between the aortic valve and the MA (along the AP direction) planes; anterior and posterior leaflets area and length, MV tenting height, tenting area and tenting volume.

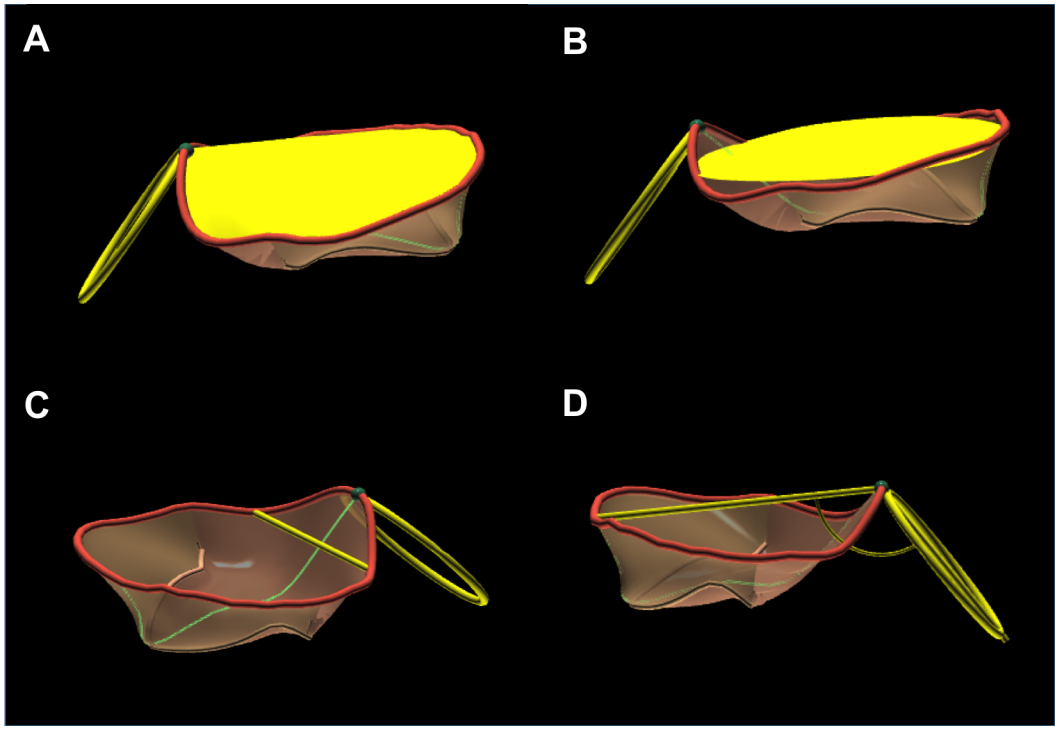

Figure 33 Mitral annulus parameters automatically analyzed at mid-systolic frame. *(A) 3D mitral annulus area, (B) mitral annulus area at the best fit plane, (C) Inter-trigonal distance, (D) Aorto-Mitral angle*

Statistical analysis

The normal distribution of the variables was checked using the Kolmogorov-Smirnov test. Continuous data are presented as mean ± standard deviation (SD) or Median (25°-75°) and categorical variables as absolute numbers and percentages, as appropriate. In the validation study, the relationship between TTE mid-systolic MA parameters measured using the two software packages, and mid-systolic and early-diastolic parameters measured using TTE and TEE data sets in the same patient, were evaluated using Pearson or Spearman correlation. Bland–Altman plots were used to assess the mean difference and the limits of agreement between them. Paired t test or Wilcoxon rank test were used, as appropriate, for comparing the MV dimension obtained by TTE and TEE data set in the same patient.

Variables were compared between IMR and nIMR patients using the unpaired t or the Mann-Whitney tests, as appropriate. Chi-square was used to compare the categorical variables. A paired t test or

Wilcoxon signed rank test was used to compare systolic and diastolic dimensions within the same subgroups, as appropriate. Percentage change of the systo-diastolic measurements was calculated.

Data analyses was performed using SPSS version 20.0 (SPSS, Inc, Chicago, IL) and GraphPad Prism V 7 (GraphPad Software, La Jolla, CA). Differences among variables were considered significant at p value < 0.05.

Results

Validation study

The TTE validation cohort included 30 patients (15 with IMR; 22 men; mean age 64±2 year) with good image quality. The temporal resolution of the 3D dataset for MV quantification was 35±3 volumes per second (vps). Close correlations and good agreements were found between the measurements obtained with the two software packages. **(Figures 34-36)**

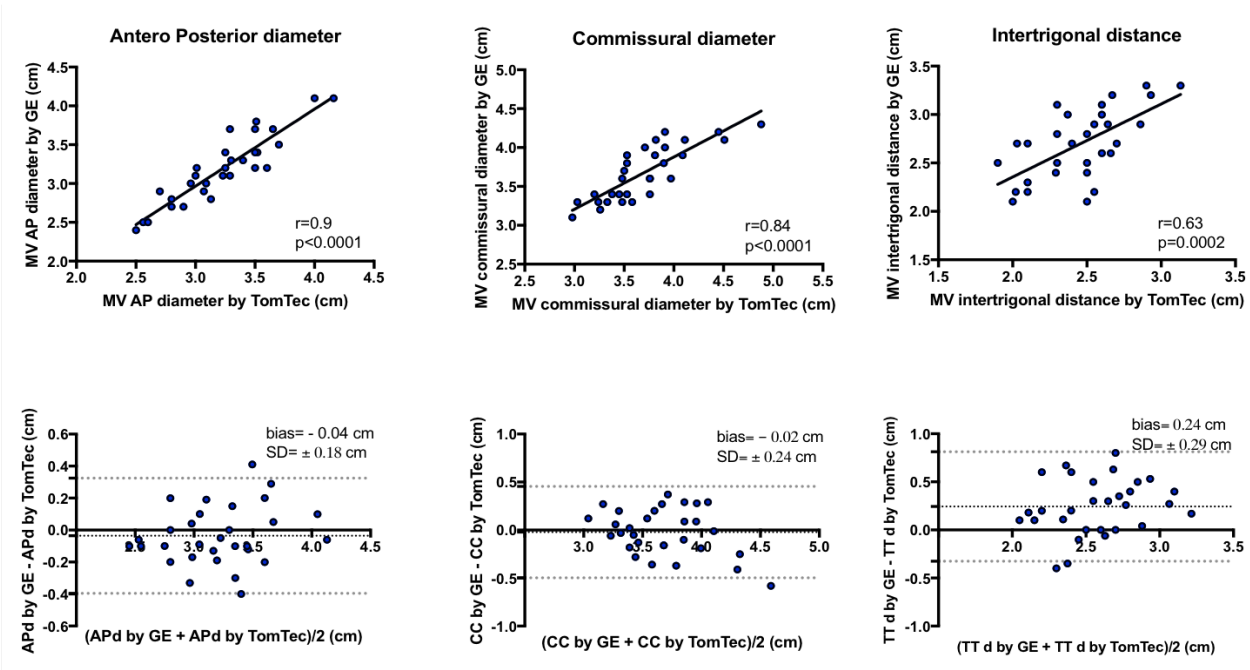

Figure 34 Comparisons of mitral annulus diameter measured by GE and TomTec software using Pearson correlation (top) and Bland–Altman (bottom) analyses

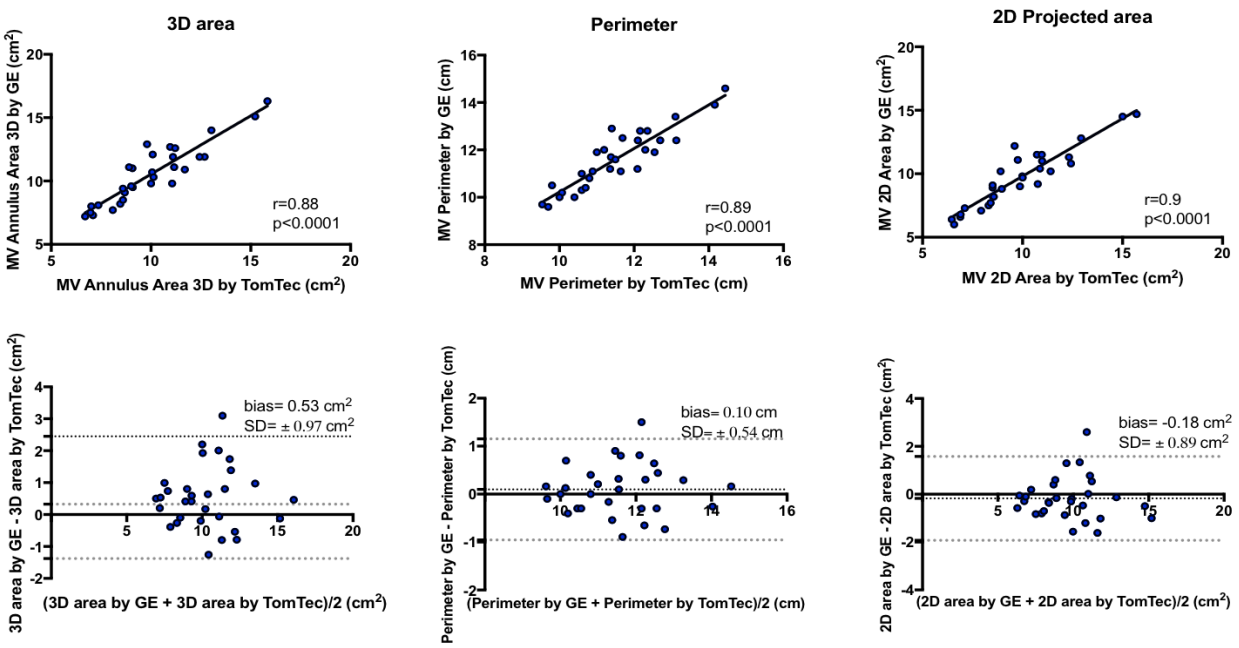

Figure 35 Comparisons of mitral annulus area and perimeter measured by GE and TomTec software using Pearson correlation (top) and Bland–Altman (bottom) analyses

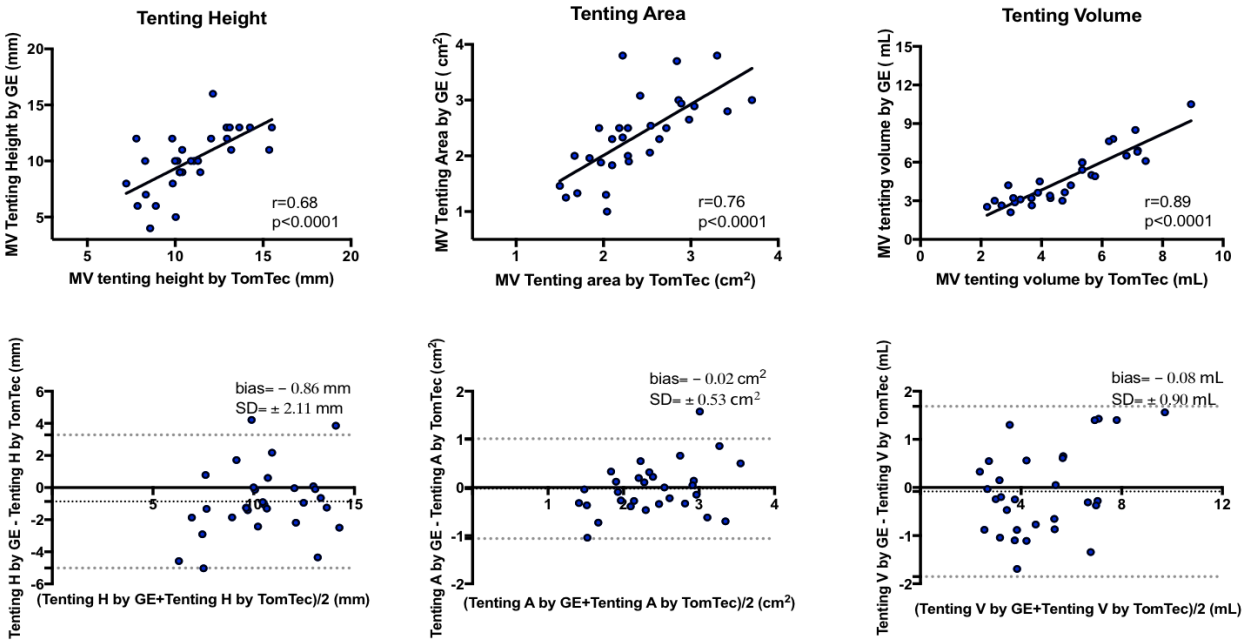

Figure 36 Comparisons of mitral annulus tenting value measured by GE and TomTec software using Pearson correlation (top) and Bland–Altman (bottom) analyses

The TEE validation cohort included 15 patients (8 with IMR; 14 men; mean age 63±15 year). As expected, both image quality (excellent quality in 75% versus 25%, respectively, p=0.009) and temporal resolution (34±15 vps versus 29±10 vps, respectively, p<0.05) were higher for TEE than TTE data sets. The mean time lapse between TTE and TEE data set acquisitions was 1(0-6) day. Measurements obtained from TEE data sets resulted in slightly larger area, perimeter and AP diameter (Table 5). However, there was a close correlation between the two techniques and the differences were not clinically relevant. Among linear dimension, ALPM, commissural diameter and diastolic inter-trigonal distance are the most similar in TEE and TTE data sets, while tenting area, tenting volume and non-planar showed the largest differences. **(Table 5) (Figure 37-41)**

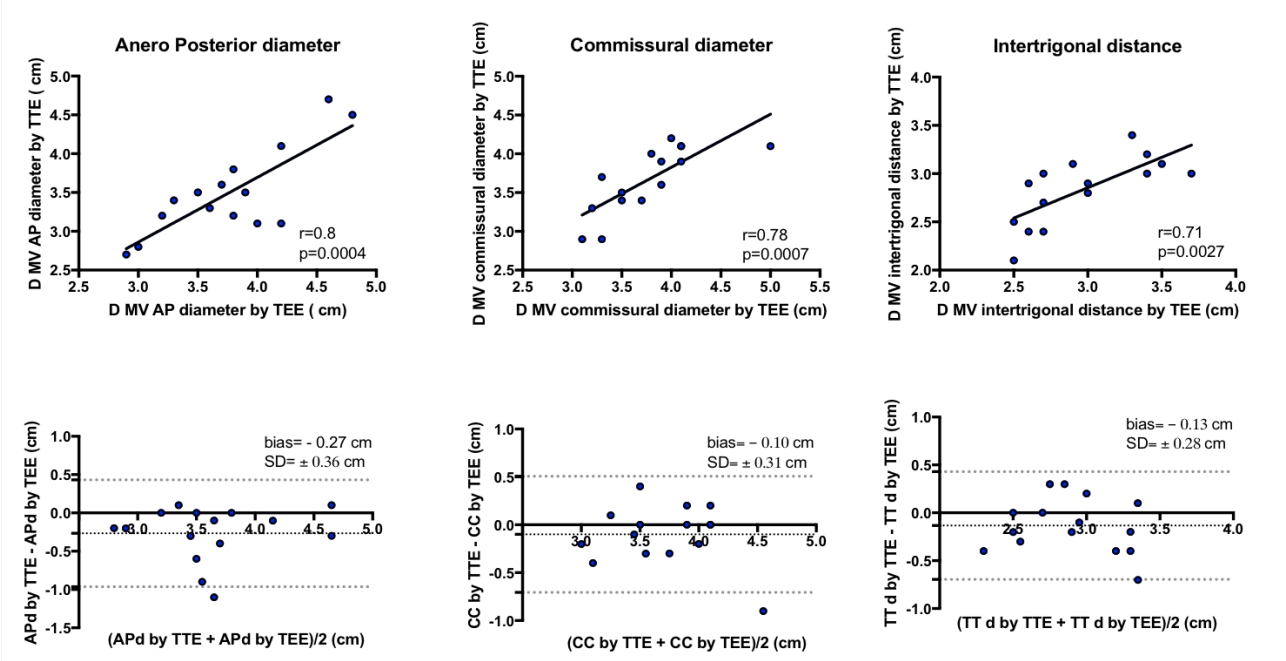

Figure 37 Comparisons of mitral annulus early-diastolic diameter measured by transthoracic and transesophageal echocardiography using the same software package using Pearson correlation (top) and Bland–Altman (bottom) analyses

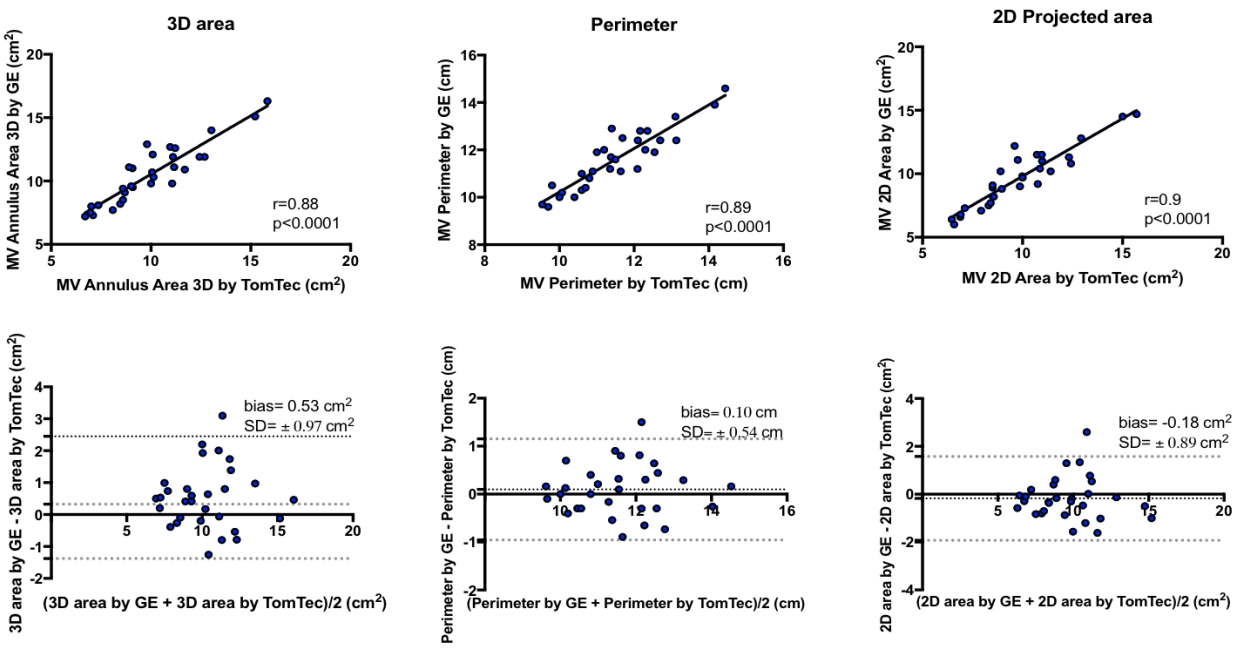

Figure 38 Comparisons of mitral annulus early-diastolic area and perimeter measured by transthoracic and transesophageal echocardiography using the same software package using Pearson correlation (top) and Bland–Altman (bottom) analyses

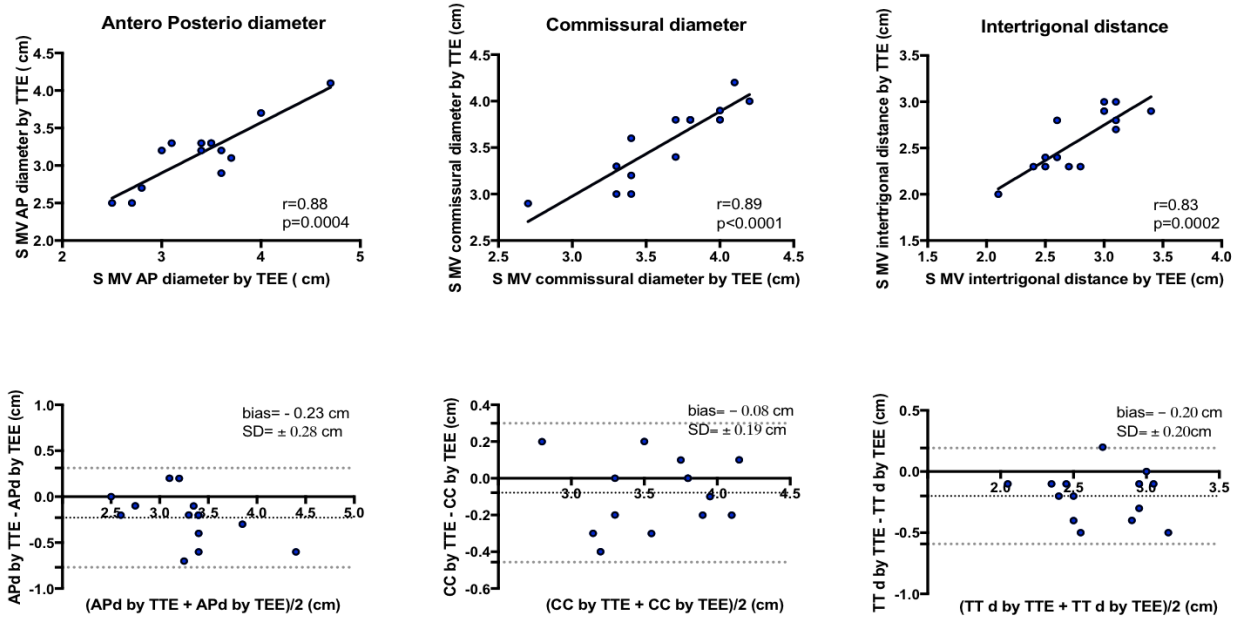

Figure 39 Comparisons of mitral annulus mid-systolic diameter measured by transthoracic and transesophageal echocardiography using the same software package using Pearson correlation (top) and Bland–Altman (bottom) analyses

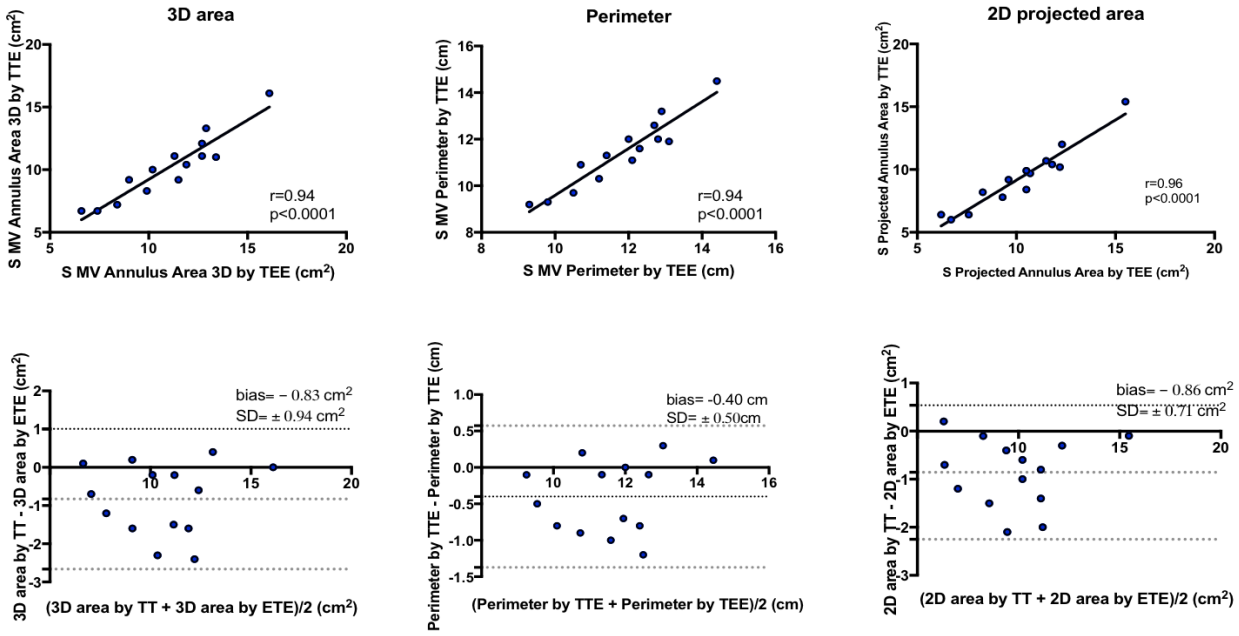

Figure 40 Comparisons of mitral annulus mid-systolic area and perimeter measured by transthoracic and transesophageal echocardiography using the same software package using Pearson correlation (top) and Bland–Altman (bottom) analyses

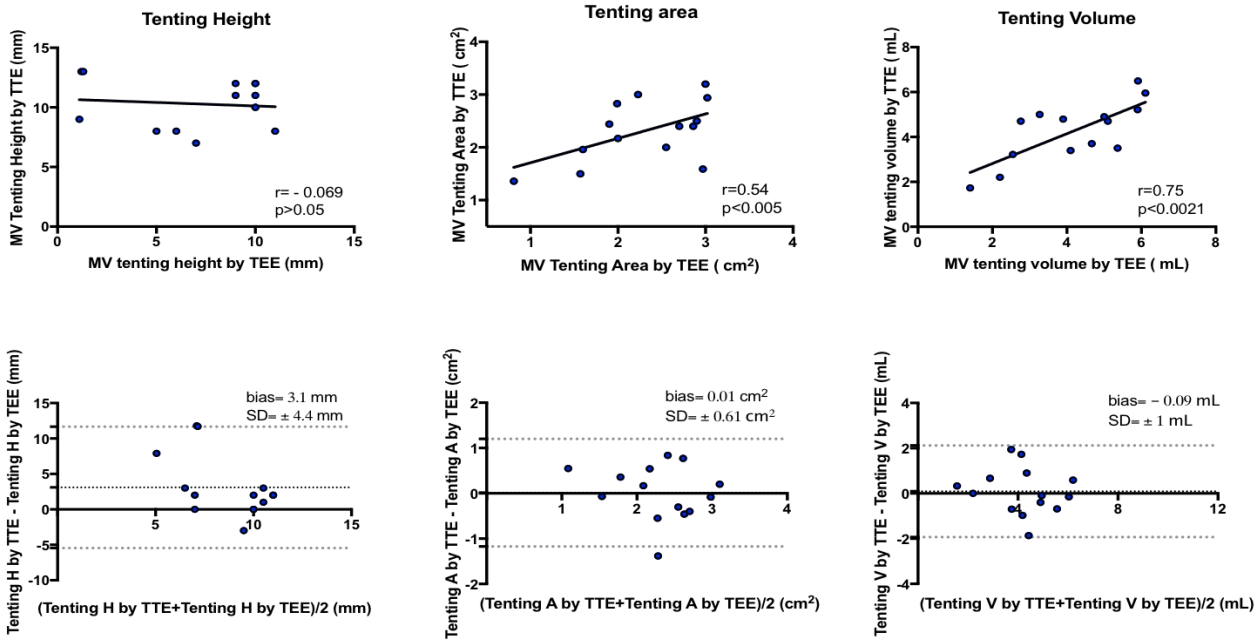

Figure 41 Comparisons of mitral annulus tenting value measured by transthoracic and transesophageal echocardiography using the same software package using Pearson correlation (top) and Bland–Altman (bottom) analyses

Table 5 Comparison of mitral annulus parameter among transthoracic and transoesophageal data sets

	Transthoracic N=15	**Transoesophageal N=15**	**p**	**r**
Diastolic dimension				
Annulus area (3D) (cm^2)	11.5 ± 3.1	12.4 ± 3.2	0.031	0.879**
Annulus best fit plane (cm^2)	10.6 ± 3.0	11.7 ± 3.1	0.016	0.869**
Annulus perimeter (cm)	12.1 ±1.7	12.6 ± 1.6	0.036	0.883**
AP diameter (cm)	3.5 ± 0.5	3.8 ± 0.5	0.012	0.799**
ALPM diameter (cm)	3.7 ± 0.5	3.8 ± 0.5	0.342	0.840**
Commissural diameter (cm)	3.7 ± 0.4	3.8 ± 0.5	0.231	0.777**
Itertrigonal distance (cm)	2.8 ± 0.3	3.0 ± 0.4	0.094	0.715**
Sphericity index	0.9 ± 0.1	1.0 ± 0.1	0.150	0.157
Annulus height (mm)	7.3 ± 1.7	6.8 ± 1.6	0.343	0.559*
Non planar angle	156 ± 13	152 ± 11	0.314	0.474
Mitro-aortic angle	131 ± 8	125 ±10	0.039	0.418
Systolic dimension				
Annulus area (3D) (cm^2)	10.2 ± 2.6	11.0 ± 2.6	0.006	0.936**
Annulus best fit plane (cm^2)	9.3 ± 2.5	10.2 ± 2.5	0.001	0.959**
Annulus perimeter (cm)	11.4 ±1.5	11.8 ± 1.4	0.010	0.943**
AP diameter (cm)	3.2 ± 0.4	3.4 ± 0.6	0.002	0.624* $^{\rho}$
ALPM diameter (cm)	3.6 ± 0.5	3.6 ± 0.4	0.329	0.857**
Commissural diameter (cm)	3.5 ± 0.4	3.6 ± 0.4	0.151	0.889**
Itertrigonal distance (cm)	2.6 ± 0.4	3.0 ± 0.4	0.000	0.830**
Sphericity index	0.9 ± 0.1	0.9 ± 0.1	0.062	0.321$^{\rho}$
Annulus height (mm)	7.0 ± 1.3	7.0 ± 1.4	0.910	0.300
Non planar angle (°)	153 ± 10	153 ± 9	0.893	0.240
Aorto-mitral angle (°)	139 ±10	129 ± 8	0.005	0.367
Tenting height (mm)	10.3 ± 2.0	7.2 ± 3.6	0.020	- 0.108
Tenting area (cm^2)	2.3 ± 0.6	2.3 ± 0.7	0.934	0.542*
Tenting volume (mL)	4.2 ±1.3	4.1 ± 1.5	0.742	0.747**

Data are expressed as Mean ± Standard Deviation. Abbreviations: ALPM, anterolateral-posteromedial, AP, antero-posterior diameter.* for correlation with $p < 0.05$; ** for correlation with $p < 0.001$; $^{\rho}$ evaluated with Sperman's correlation

Comparison of mitral annulus geometry between ischemic and non-ischemic mitral regurgitation

We enrolled 94 patients, 41 (43,6%) with IMR and 53 (56,4%) with nIMR. Patients with IMR were more frequently male and had a higher incidence of hypertension, diabetes and dyslipidemia. **(Table 6)** The severity of MR was comparable between the two groups. **(Table 7)** Although patients in both groups showed severe LV dilatation and dysfunction, patients with IMR had a higher LVEF (31 (26-38)% versus 28 (22-32)%, p=0.030) and LV wall motion score index (2.1±0.3 versus 1.9± 0.6, p=0.021). **(Table 7)**

Temporal resolution of the 3D dataset dedicated for MV quantification was higher in IMR than in nIMR patients (33±14 vps versus 40±16 vps, p=0.023). All data sets had enough good quality for the quantitative analysis. The image quality was graded excellent in 47 patients (50%), good in 32 (34%), and fair in 15 (16%) and it was comparable between IMR and nIMR patients (p=0.634).

Table 6 Demographics and clinical characteristics

	Ischemic Mitral Regurgitation N=41	**Non Ischemic Mitral Regurgitation N=53**	**p**
Age (years)	69 (63-75)	64 (55-72)	0.081
Men (%)	**35 (85)**	**35 (66)**	**0.033**
Body surface area (m^2)	1.8 (1.7-1.9)	1.9 (1.7-2.0)	0.374
Heart rate (bpm)	71(59-85)	75 (65-86)	0.237
Systolic blood pressure (mmHg)	110 (100-120)	100 (95-115)	0.340
Diastolic blood pressure(mmHg)	65(60-71)	65 (60-70)	0.233
Hypertension	**32 (80%)**	**25 (48.1%)**	**0.002**
Diabetes	**15 (37.5%)**	**8 (15.4%)**	**0.015**
Dyslipidemia	**30 (75%)**	**22 (42.3%)**	**0.002**
Smokers	23 (57.5%)	24 (46.2%)	0.280
Resynchronization therapy	8 (20%)	17 (32.7%)	0.175

Data are expressed as Median (25°-75°) or Number (%).

Using conventional two-dimensional echocardiography MV geometry parameters, patients with nIMR showed larger AP diameter both in diastole (41±7 mm in nIMR versus 38±6 mm in IMR, p=0.029) and in systole (37± 6 mm in nIMR versus 34±4 mm in IMR, p=0.024). Conversely, CC diameter (43±8 mm in nIMR versus 39±9 mm in IMR, p=0.088), tenting height (9±3 mm in nIMR versus 8.5±3 mm in IMR, p=0.180) and tenting area (1.9 ±0.7 cm^2 in nIMR versus 1.7±0.6 cm^2 in IMR, p=0.189) were similar between the two groups.

Table 7 Echocardiography characteristics

	Ischemic Mitral Regurgitation N=41	**Non Ischemic Mitral Regurgitation N=53**	p
MR Vena contracta (mm)	7 (6-8)	7 (6-8)	0.658
MR PISA radius (mm)	7 (6-8)	8 (7-9)	0.138
MR EROA (mm2)	2 (2-3)	2.1(2-3)	0.421
MR R Vol (mL)	38 (28-58)	38.5 (29-47.7)	0.803
sPAP	47 (35-56)	44 (35-49)	0.211
TR severity	Trivial 6 (11.3%) Mild 29 (54.7%) Moderate11 (20.8%) Severe 7 (13.2%)	Trivial 6 (15.4%) Mild 20 (51.3%) Moderate10 (25.6%) Severe3 (7.7%)	0.753
AR severity	None 25(49%) Trivial 13(25%) Mild 12(23.5%) Moderate 1 (2%)	None 25 (65%) Trivial 6 (15%) Mild 9 (22.5%) Moderate 0 (0%)	0.437
LV EDV (ml/m^2)	134 (114-153)	143(116-178)	0.078
LV ESV (mL/m^2)	96 (68-109)	105 (78-135)	0.075
Ejection Fraction (%)	**31 (26-38)**	**28 (22-32)**	**0.030**
Indexed LA volume (mL/m2)	**60 (51-68)**	**70 (53-91)**	**0.031**

Data are expressed as Median (25°-75°) or Number (%).
Abbreviations: AR, aortic regurgitation; EROA, effective regurgitant orifice area; LA, left atrial; LV EDV, left ventricular end-diastolic volume, LV ESV, left ventricular end-systolic volume; MR, mitral regurgitation; PISA, proximal isovelocity surface area; R Vol, regurgitant volume; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

At 3DE analysis, both subgroups had similar diastolic geometry of MA, even though all MA dimensions were slightly larger in nIMR. nIMR patients showed larger mid-systolic 3D area and perimeter of the MA with longer leaflets. However, the area of the annulus at the best fit plane, and all diameters (AP, CC, ALPM diameter and trans-trigonal distance) did not differ between IMR and nIMR patients. Tenting height and area did not differ between IMR and nIMR patients, whereas tenting volume, annulus height and aorto-mitral angle were larger in nIMR patients. **(Table 9)**

Mitral annulus dynamics

In both groups, MA significantly reduced its dimensions in systole (except for CC diameter) with similar percentage change of the measurement in both groups (p>0.05). **(Table 8 and 9)** During systole, the MA mitral-aortic angle flattens, while the non-planarity angle becomes more acute.

Table 8 Fractional changes of the mitral annulus parameters between diastole and systole

	Ischemic Mitral Regurgitation N=41	**Non Ischemic Mitral Regurgitation N=53**	**p**
MA area (3D) fraction (%)	-6 (-11.7 – -1.8)	- 4.3 (-9.8 – -1.3)	> 0.05
MA best fit plane fraction (%)	-6.3 (-13 – -4)	-6.7 (-11.4 – -1.8)	> 0.05
MA perimeter fraction (%)	-3.2 (-5.8 – - 0.4)	-2.1 (-4.6 – -0.8)	> 0.05
AP diameter fraction (%)	-7.4 (-11.4 – -2.4)	-5.9 (-11.2 – -1.3)	> 0.05
ALPM diameter fraction (%)	-2.9 (-6.9 – -0.0)	0.0 (-7.3 – 0.0)	> 0.05
CC diameter fraction (%)	-2.6 (-5.5 – 2.9)	0.0 (-4.7 – 2.7)	> 0.05
TT distance fraction (%)	-4.8 (-12.4 – 0.0)	-3.1 (-10 – 3.8)	> 0.05
Non planar angle fraction (%)	-2 (-6.3 – 2.5)	-2.4 (-5.6 – 2)	> 0.05
Aorto-mitral angle fraction (%)	3.7 (-2.5 – 8.4)	3.4 (0 – 8.4)	> 0.05

Data are expressed as Median (25°-75°).
Abbreviations: ALPM, anterolateral-posteromedial; AP, antero-posterior diameter; CC, commissural; MA, mitral annulus; TT, trans-trigonal.

Table 9 Three-dimensional mitral valve dimension

	Ischemic Mitral Regurgitation N=41	Non Ischemic Mitral Regurgitation N=53	p
Diastolic dimension			
Annulus area (3D) (cm^2)	10.7 ± 2.5*	11.6 ± 2.7*	0.124
Annulus best fit plane (cm^2)	9.9 ± 2.3*	10.7 ± 2.5*	0.135
Annulus perimeter (cm)	11.7 ±1.4*	12.2 ± 1.4*	0.111
AP diameter (cm)	3.3 ± 0.4*	3.5 ± 0.5*	0.072
ALPM diameter (cm)	3.6 ± 0.4*	3.8 ± 0.5*	0.129
Commissural diameter(cm)	3.6 ± 0.4	3.7 ± 0.4	0.300
Itertrigonal distance (cm)	2.7 ± 0.4*	2.8 ± 0.3*	0.374
Annulus height (mm)	6.3 ± 1.7*	6.8 ± 1.7*	0.144
Sphericity index	0.9 ± 0.1*	0.9 ± 0.1*	0.963
Non planar angle (°)	156 ± 11*	153 ± 10*	0.232
Anterior leaflet area (cm^2)	7.5 ±1.6*	8.0 ± 1.6*	0.142
Posterior leaflet area (cm^2)	7.2 ±2.3*	7.5 ± 2.1*	0.413
Anterior leaflet length (cm)	2.9 ±0.4	3.3 ±0.9*	0.102
Posterior leaflet length (cm)	1.6 ± 0.4*	1.7 ± 0.6*	0.319
Aorto-mitral angle (°)	131 ± 9*	135 ± 11*	0.115
Systolic dimension			
Annulus area (3D) (cm^2)	**9.8 ± 2.3**	**10.8 ± 2.7**	**0.046**
Annulus best fit plane (cm^2)	9 ± 2.1	9.9 ± 2.5	0.063
Annulus perimeter (cm)	**11.2 ±1.3**	**11.8 ± 1.5**	**0.048**
AP diameter (cm)	3.1 ± 0.4	3.2 ± 0.5	0.063
ALPM diameter (cm)	3.5 ± 0.4	3.7 ± 0.5	0.065
Commissural diameter(cm)	3.5 ± 0.4	3.7 ± 0.4	0.130
Itertrigonal distance (cm)	2.5 ± 0.3	2.7 ± 0.3	0.051
Annulus height (mm)	**6.7 ± 1.6**	**7.5 ± 1.9**	**0.047**
Sphericity index	0.9 ± 0.08	0.9 ± 0.1	0.598
Non planar angle (°)	153 ± 11	150 ± 10	0.268
Anterior leaflet area (cm^2)	**6.5 ± 1.6**	**7.4 ± 1.7**	**0.006**
Posterior leaflet area (cm^2)	**5.7 ± 1.7**	**6.5 ± 1.9**	**0.049**
Anterior leaflet length (cm)	**2.8 ± 0.6**	**3 ± 0.4**	**0.022**
Posterior leaflet length (cm)	**1.3 ± 0.4**	**1.5 ± 0.8**	**0.022**
Aorto-mitral angle (°)	**135 ± 10**	**141 ± 11**	**0.011**
Tenting height (mm)	9.3 ± 2.6	10.3 ± 2.8	0.082
Tenting area (cm^2)	2.2 ± 0.7	2.4 ± 0.8	0.141
Tenting volume (mL)	**4 ±1.7**	**4.7 ± 1.7**	**0.047**

Data are expressed as Mean ± Standard Deviation.
Abbreviations: ALPM, anterolateral-posteromedial, AP, antero.posterior diameter.
* Statistical difference vs systolic dimension

Discussion

1) Preclinical study assessing the feasibility and early safety of a novel mitral valve self-expandable prosthesis

The pre-clinical assessment of the safety and feasibility of the Epygon transcatheter bioprosthetic mitral valve implantation showed favorable results. In the sheep model, the implantation was feasible across different anatomic subsets and short-term safety was acceptable. The sheep model is considered the gold standard for testing the performance of novel prostheses at long-term follow-up because tissue leaflets are prone to accelerated calcification and degeneration. In addition, findings in the sheep model can be more easily generalized because the MA shape is comparable to the adult human and does not change significantly over a 5-month period compared with the swine model.[6]

The Epygon valve is a catheter-based self-expanding mitral bioprosthesis specifically designed to fit the complex anatomic structure of the mitral apparatus. Among the singular characteristics of the Epygon prosthesis, the asymmetric nitinol stent and the advanced mono-leaflet structure need to be mentioned. These two key components are designed to replicate the normal anatomy and function of the MV, which has indeed D-shape and larger anterior leaflet.

Each transcatheter mitral valve prosthesis has some unique features but also generally shares some characteristics with others. As the Epygon prosthesis, also the Tiara, Tendyne and Caisson systems have a D-shaped stent. The Tendyne and Caisson prostheses are characterized by a D-shaped outer frame that anchor the native mitral valve annulus and a circular inner frame with a three porcine pericardium leaflets. Tiara prosthesis has three leaflets made of bovine pericardium and is characterized by an atrial skirt and a ventricular anchoring system. The Epygon prosthesis has anterior and posterior paddles to catch MV leaflets as the Tiara and the Fortis systems. As many other competitor bioprostheses, the Epygon was primarily developed for the TA approach; however TS implantation is under development.

2) Evaluation of the prosthesis function by hemodynamic surrogate parameters and blood flow characteristics

The favorable post-procedural hemodynamic results were evaluated by using Doppler quantification and both 2D and 3D echocardiography as described in the proper section.

The analysis was complemented by echocardiography particle imaging velocimetry (Echo-PIV) which is an emerging imaging technique enabling the assessment of the intraventricular fluid dynamic and the characterization of diastolic vortex formation as expression of the LV filling efficiency.[98,99] In the LV, the laminar mitral inflow is converted into a vortex at the tips of the mitral valve leaflets which maintains the momentum of the blood flow and allows its smooth redirection towards the outflow tract during systole with minimal generation of turbulence and consequent avoidance of large loss of kinetic energy.[100,101] Because of fluid viscosity, a blood flow vortex loses energy. The energy loss is particularly high if there are rapid changes in vorticity (high pulsatility) or if many small vortices interact (turbulence).[102] In case of energetically unfavourable conditions, kinetic energy gets lost with higher demand to the LV muscle in the following cardiac cycle.[102]

Faludi and colleagues assessed vortex formation in healthy subjects and the effects of different types of prosthetic valves on intraventricular flow patterns and flow-mediated energy dissipation.[102] In healty subjects, vortex detaches from the anterior leaflet of the mitral valve at the beginning of early-diastolic phillling, rotates clockwise in the 3- chamber view and fills almost the entire LV by the end of early-diastolic phillling. At the very end of diastole, a single large vortex is present, and blood is smoothly redirected toward the outflow tract for the following systole. In patients with mechanical bi-leaflet valve in anatomic orientation (hinge positions approximating commissures of the previous native valve), the resulting vorticity pattern is opposite to that seen in healthy hearts, characterized by a large counterclockwise rotating vortex. The flow through a bioprosthesis generates a central jet directed toward the apex, with loss of the symmetry of flow pattern and crossing with preceding

inflow area of the outflowing blood during systole. Moreover, in patients with bioprosthetic and mechanical valves, the parameters of energy dissipation were higher than in healthy subjects.[102,103]

Our preliminary analysis on 14 sheep seems supporting the hypothesis that the Epygon bioprosthesis by means a physiological-like inflow area respects a normal flow pattern towards the LV. Similar to previous findings,[102,103] we showed a significant increase in energy dissipation (energy loss) after device implantation, though the amount of loss was 30% lower than elsewhere reported.[103]

Recent fluid dynamic data demonstrated that in normal LV the blood flow is characterized by a longitudinal alignment along the base–apex direction of the intraventricular hemodynamic pattern in compliance with the emptying-filling process.[104] Conversely, HF patients or non-responders to the resynchronization therapy show an irregular vortex formation with local stagnation resulting in transversal forces and loss of the physiological longitudinal orientation of the intraventricular velocities.[98,99,105]

After implantation of the Epygon bioprosthesis, the dominant direction of blood flow momentum presented a statistically significant variation, though the magnitude of the change was trivial. This finding could be partially explained by the presence of suture stiches used for trans-apical access closure that did not allow placing the probe exactly in the same point before and after intervention with unavoidable influences on the assessment of the orientation of the LV long axis. In addition despite the observed variation, the main axis of blood flow still remained roughly parallel to the LV axis as expression of an efficient pattern within the LV.

3) Assessment of the mitral valve anatomy using three-dimensional echocardiography in patients with functional mitral valve regurgitation focusing on the anatomical implications for prosthesis-based transcatheter approach

In the present study, we used 3D TTE to compare MA geometry in patients with severe ischemic and non-ischemic FMR, who are potential candidates for TMVR.

The main findings of our study were in patients with FMR: i, diastolic MA geometry is similar in both nIMR and IMR patients; ii, systolic MV geometry significantly differs between the groups.

Validation study

Multimodality imaging represents the gold standard for planning transcatheter mitral valve procedure, TEE and multi-slice computed tomography (MSCT) playing the major role.[106] Due to longer survival of patients with chronic heart diseases and progressive aging of the general population, the number of patients who could benefit of TMVR is likely to increase, and 3DTTE will be of paramount importance as a screening tool for the analysis of MV geometry. Previous clinical studies assessing MA geometry used 3DTEE data sets[107,108] to obtain adequate spatial and temporal resolution for quantitative analysis of the MV. However, the progressive improvement of 3DE technology allows to obtain better and better quality 3DE data sets with TTE, too. Moreover, feasibility and cost/effectiveness considerations suggest that TTE approach would be better suited to screen potential candidates to TMVR. Accordingly, we decided to explore the use of 3DTTE data sets perform quantitative analysis of the MV in patients with FMR. In our patients, MA dimensions obtained from TTE datasets were similar to those obtained with the 3D TEE approach in the validation study.

Comparison of mitral annulus dimension between ischemic and non-ischemic mitral regurgitation

We focused our study on patients with FMR because they represent the main potential target of new TMVR. Previous echocardiographic studies compared MA geometry between FMR patients (without distinction among ischemic and non-ischemic etiology) and normal subjects[109,110], patients with organic MV disease[111,112] or hypertrophic cardiomyopathy[113]. Other studies selected only IMR patients to compare with healthy subjects [114] or myxomatous MR.[107] The few studies that analyzed the possible differences between IMR and nIMR[11-14] included a limited number of patients and were focused only on MA size (annulus area and diameters), without any information about the MV geometry (MA area at the best fit plane, mitro-aortic angle, length of the anterior leaflet) which are crucial to select patients for TMVR.[106]

In this study, we reported all MV anatomical and geometrical features that should be assessed before TMVR[9,115] and demonstrated that patients with severe IMR and nIMR have similar, symmetrical, diastolic (maximal) MA dimension. The 3D MA area obtained from our patients were comparable with the maximum MA surface area reported by Veronesi et al.[13] in a smaller group of patients using TTE 3DE datasets. Our results are in agreement to those reported by Daimon et al. [11] who showed that diastolic MA diameters did not differ among IMR and nIMR. However, the actual MA sizes in our patients were slightly larger than in their. This finding could be partially explained by the different time point selected for the analysis (mid-diastolic phase, compared to early-diastole in our study).

While in our study mid-systolic 3D annulus area and perimeter are significantly larger in patients with nIMR, MA area at the best fit plane and MA diameter are similar. It has been suggested that the projected 3D MA area at the level of the best fit plane is the most reliable parameter of MA geometry to be used for planning TMVR compared to the saddle-shaped 3D area.[115] Though, our MA area at the best fit plane resulted smaller than the mean projected MA area measured in a recent MSCT study [116] on 32 patients with FMR of different etiologies and severity, it is already known that 3DE can underestimate measurement compared with MSCT due to its suboptimal lateral resolution in the coronal plane.[117]

A new D-shaped MA segmentation developed by Blanke et al.[118], with the truncation of anterior saddle horn at the level of inter-trigonal line, has been used to select candidates to Tiara [6], Tendyne[8] and Intrepid[7] valve implant. This method was also recently applied by Mak et al. [112] using 3D TEE with comparable results, but it is unclear at this early stage of TMVR experience whether this is the best parameter to size the prosthesis for TMVR interventions. [119]

Left ventricular out flow tract (LVOT) obstruction is a possible complication related to TMVR that can be predicted during procedure planning because it is related to the design of the prosthesis and patient anatomy (interventricular septal dimension, LV size, aorto-mitral angle, anterior leaflet length). MSCT virtual modelling of the prosthesis is able to "create" and quantify the neo-LVOT to predict the risk of LVOT obstruction.[92] 3DE allows the measurement of both the aorto-mitral angle (the angle between the aortic valve and the MA along the AP direction) and anterior leaflet length. None of the previous MSCT nor the 3DE studies reported these parameters in patients considered for TMVR. In our study we found that nIMR group presented significantly wider aorto-mitral angle that balance the potential higher risk of LVOT obstruction due to longer and larger anterior leaflets in these patients.

Mitral annulus dynamics

MA is dynamic structure characterized by an annular contraction between mid-diastole to early-systole followed by a progressive expansion throughout the second half of the systole that reaches its maximum dimension during early diastolic filling.[13,120] These changes, although less pronounced than in normal subjects, have been reported also in patients with IMR[107,121] and nIMR[13]. We found that in patients with severe FMR, MA is significantly smaller in mid-systole compared to early diastolic phase. This findings underly the necessity of a multiphasic MA assessment to select patients for TMVR [9], but the few investigations that analyzed MA dimension in moderate or severe FMR (potentially candidates for TMVR), reported only the measurement in one phase of the cardiac cycle.[13,14]

In our study, the non-planarity angle, a parameter describing the ‘‘saddle-shaped’’ morphology of the MA, become more acute (the annulus increases its “*saddleness*”) whereas the mitral-aortic angle flattens, in systole. This finding, are in contrast to previous study of Veronesi et al. [122] in normal subjects, and probably this alteration may contribute to pathophysiology of FMR.

Implications for trans-catheter mitral valve selection

TMVR represents a promising option for patients with severe FMR, and assessment of MA dimension and geometry is of paramount importance to size the device and also to plan future development of new prostheses. We found that, patients with IMR and nIMR have similar MA geometry, supporting the concept that there is no need of different prosthesis sizing according to etiology of FMR. However, we found that nIMR patients had significantly larger and longer anterior mitral leaflet, that could increase the risk of LVOT obstruction. Therefore, for nIMR patients it could be more appropriate to select a device that has an anterior hook to fix the anterior leaflet of the native MV. On the other hand, nIMR patients showed a wider aorto-mitral angle that could counterbalance the higher risk of LVOT obstruction carried by longer anterior leaflet. Probably, this sub-group of patients would be eligible also for devices that have larger protrusion or flaring into LV.

The significant change of MA during the cardiac cycle, also preserved in patients with severe FMR, stresses the need to evaluate accurately the smallest MA dimension in order to reduce the risk of excessive stress of the prosthesis frame by MA.

Study limitations

We acknowledge certain limitations of our study. First, to obtain all the measurements needed to plan TMVR from 3DE data sets, we used a new MV software package that was not previously validated. To overcome this limitation, we compared the measurements obtained with the new software package with those obtained from the same data sets using a validated software[95] with a close correlations and

good agreement. However, we did not compare our measurement with MSCT, which represents the current gold standard for patient selection for TMVR.

Secondly, currently available 3DE software packages allow MV dynamic analysis only during the systolic phase of the cardiac cycle; while mid-systole could be defined by the operator according to MV opening and closure or automatically by the software (as mid-way between R and T waves on the ECG tracing), early-diastole has to be manually identified by the operator with an increased possibility of errors. Current literature reports contradicting data about the moment when MA reaches its maximum and minimum sizes, however the importance of definition of maximum MA dimension is of paramount importance for accurate device's sizing and emphasizes the need of multiphasic annular measurement.

Conclusions

The treatment of severe MR in patients with high surgical risk represents a new challenge for transcatheter therapeutic approaches. Novel TMVR systems can represent the answer for most of patients with complex MV anatomy, advanced disease, severe leaflet tethering or MA dilation. Early TMVR clinical reports showed promising results and suggested that advances in transcatheter strategies technology can generate in the incoming future valid therapeutic alternatives to the traditional surgical intervention.

Our initial preclinical experience with the novel bovine tissue mono-leaflet D-shaped nitinol frame transcatheter self-expandable mitral valve bioprosthesis by TA access showed that the correct implantation is feasible, safe, and associated with good post-procedural hemodynamic results. The application of advanced echocardiography guided valve orientation and positioning during the procedure, supported continuous refinements for the improvement of the bioprosthesis, and provided an useful tool for the assessment of the performance after implantation. The results of the ongoing preclinical study with the Epygon bioprosthesis are intended as background for future applications in the human.

The reported MA geometry in a relatively large group of patients with severe FMR, potentially candidates for TMVR, represents an useful information for transcatheter MV prosthesis design and patient selection. Patients with ischemic and non-ischemic etiologies of FMR have similar maximum dimensions, yet systolic differences between the two groups should be taken into account to tailor prosthesis selection.

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