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CLINICAL RESEARCH
Valvular heart disease

Transcatheter mitral valve repair for functional mitral regurgitation using the Cardioband system: 1 year outcomes

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Aims The Cardioband™ (Edwards Lifesciences) is a transcatheter implant designed to reduce mitral annulus size and mitral regurgitation (MR) severity. We report the 1-year outcomes of consecutive patients who underwent the Cardioband procedure between 2013 and 2016.

Methods and results Sixty patients with moderate or severe secondary MR (72 ± 7 years, 60% ischaemic origin) on guideline-recommended medical therapy were treated and analyzed at 11 European institutions. There were two in-hospital deaths (none device-related), one stroke, two coronary artery complications, and one tamponade. Anchor disengagement, observed in 10 patients (all but one in the first half of the population), resulted in device inefficacy in five patients and led to device modification half way through the study to mitigate this issue. Technical, device, and procedural successes, assessed based on Mitral Valve Academic Research Consortium (MVARC) criteria, were 97% (58/60), 72% (43/60), and 68% (41/60), respectively. At 1-year, overall survival, survival free of readmission for heart failure, and survival free of reintervention (performed in seven patients) were 87%, 66%, and 78%, respectively. In the overall population, MR grade at 12 months was moderate or less 61% and moderate or less in 95% of the 39 patients who underwent a transthoracic echocardiography at 1-year [but worsened by at least one grade in 11 patients (22%)]. Functional status (79% vs. 14% in New York Heart Association Class I/II), quality of life (-19 points on the Minnesota Living with Heart Failure Questionnaire score), and exercise capacity (+58 m by 6MWT) improved significantly (all $P < 0.01$).

Conclusion In this multicentre trial, the Cardioband mitral system demonstrated reasonable performance and safety. At 1 year, most patients had moderate or less MR and experienced significant functional improvements. A randomized controlled trial is underway to demonstrate the impact of Cardioband in patients on guideline-directed medical therapy.

Keywords Mitral regurgitation • Transcatheter therapy

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Introduction

Mitral regurgitation (MR), along with aortic valve stenosis, is the most prevalent valvular heart disease.[1,2] Secondary MR is the consequence of left ventricular (LV) dysfunction and remodelling whereby enlargement of the left ventricular chamber and dilation of the mitral valve annulus results in malcoaptation of leaflets, while leaflets and chordae remain structurally normal.[3]

While the presence and severity of MR are widely accepted prognostic factors for ischaemic and dilated cardiomyopathy,[5] it is not well established whether secondary MR is the cause or a marker of this adverse prognosis. Management of patients with secondary MR relies first on optimal medical management including cardiac resynchronization and/or on coronary revascularization when indicated.[4] The benefit of correcting secondary MR and the optimal correction modality remain debated[6,7] despite surgical series and randomized controlled trials performed by the Cardiothoracic Surgical Trials Network (CTSN).[8–11] A potential explanation is that the benefit of surgical correction of secondary MR is outweighed by high operative mortality and morbidity rates in this high-risk patient population. Innovative and less invasive techniques to correct MR, namely transcatheter therapies, represent a potential solution to this dilemma. The Cardioband™ Mitral Valve Reconstruction System (Edwards Lifesciences) is a transcatheter direct annuloplasty implant designed to reduce the mitral annulus to minimize regurgitation. It is delivered via a transseptal approach and tailored to reduce annular diameter on a beating heart based on individual patient needs. In the present study, we report outcomes up to 1 year of all consecutive patients who underwent the Cardioband customized annular reduction procedure between 2013 and 2016 which led to the CE approval of the device.

Methods

Trial design and population

The study is a single-arm, prospective multicentre trial enrolling patients at 11 European institutions. Key inclusion criteria were age >18 years, symptomatic patients with at least moderate or severe secondary MR and high surgical risk as assessed by the local heart team. Key exclusion criteria were primary MR, endocarditis, systolic pulmonary artery pressure >70 mmHg, left ventricular ejection fraction <25%, LV end-diastolic diameter >70 mm, heavily calcified annulus or leaflets, coronary artery disease requiring revascularization, cardiac resynchronization therapy (CRT) within 3 months, renal insufficiency requiring dialysis, life expectancy of less than 12 months, stroke within 6 months or severe carotid stenosis, contraindication to transoesophageal echocardiography (TOE), and interatrial septum not suitable for transseptal puncture. All patients were in stable condition with optimal guideline-recommended medical therapy, including cardiac resynchronization if indicated, for at least 3 months.[4]

After verification of eligibility criteria, a written informed consent was obtained for both the procedure and the use of data for research, and the screening process was completed using transthoracic echocardiography (TTE), TOE, and multiphasic cardiac computed tomography (CT). A coronary angiography was systematically performed to exclude patients in need of revascularization. Patients were also excluded if the mitral valve anatomy was deemed inappropriate, such as extreme or highly asymmetric tenting with significant restriction of posterior leaflet mobility or close proximity of the circumflex artery to the planned location of device anchors.

Echocardiographic evaluations were performed at baseline, discharge, 30 days, 6 months, and 12 months. Functional status (New York Heart Association (NYHA) class), exercise capacity (6 minute walk test (6MWT)) and quality of life [Minnesota Living with Heart Failure Questionnaire (MLHFQ)] were assessed at baseline, 6 and 12 months.

The Cardioband mitral valve reconstruction system and procedure

The device and the procedure have been previously described.[12] Briefly, the Cardioband implant is a polyester sleeve with radiopaque markers spaced 8 mm apart containing a pre-mounted contraction wire connected to an adjusting spool. The device is delivered through a venous femoral puncture and a 25 Fr transseptal steerable sheath. The optimal position of the transseptal puncture is determined by CT analyses for each patient. Twelve to seventeen anchors are implanted through the sleeve. The length of the implant is chosen based on the mitral annulus perimeter (length of the posterior annulus from the left to the right trigone) measured using CT and commercially available software. The number of anchors is determined by the length of the band. The procedure is performed under general anaesthesia guided by 3D TOE and fluoroscopy. The first anchors are implanted as anterior as possible to the lateral commissure, and the device is progressively deployed posteriorly up to the medial commissure. A coronary angiography is recommended before releasing the first anchors to rule out potential circumflex coronary artery injury. For each anchor implantation and before release, a pull test is performed under TOE and fluoroscopic guidance to ensure proper anchoring. Once the last anchor is delivered, a size adjustment tool is inserted, and the implant is then contracted. Annulus and MR reduction are assessed using TOE under general anaesthesia and beating heart conditions. Optimal cinching /contraction was decided based on achievement of maximal MR grade reduction without increasing mitral valve tethering. Once the optimal reduction is reached, the delivery system is disconnected from the device, and wires and guides are removed.

Echocardiographic evaluation

Transthoracic echocardiography and TOE play a key role from the screening phase to the procedural guidance and the evaluation of the results. All echocardiographies were reviewed and analysed by an independent echocardiographic core lab (Paul Grayburn, MD, Baylor Health, Dallas, TX, USA). The aetiology of the regurgitation was confirmed by the core lab prior to implantation. Mitral regurgitation quantification was performed using the proximal isovelocity surface area (PISA) method [calculation of effective regurgitant orifice (ERO) and regurgitant volume (RVol)]; MR severity was graded as mild, moderate, or severe using an integrative approach as recommended in current guidelines.[13] Left ventricular volume and ejection fraction were assessed based on the biplane Simpson method. Systolic pulmonary artery pressure was calculated based on peak tricuspid regurgitation velocity. Mitral annulus diameter was measured in 4-chamber views.

Study endpoints

Safety, performance, and efficacy of the device were assessed. Technical success, device success, and procedural success were defined according to Mitral Valve Academic Research Consortium (MVARC).[14,15] Technical success, assessed at exit from the catheterization laboratory, was defined as absence of procedural mortality, successful access, delivery, deployment at the correct and intended position, and retrieval of the device without need for emergency surgery or intervention. Acceptable device success was defined at 30 days by the absence of procedural mortality or

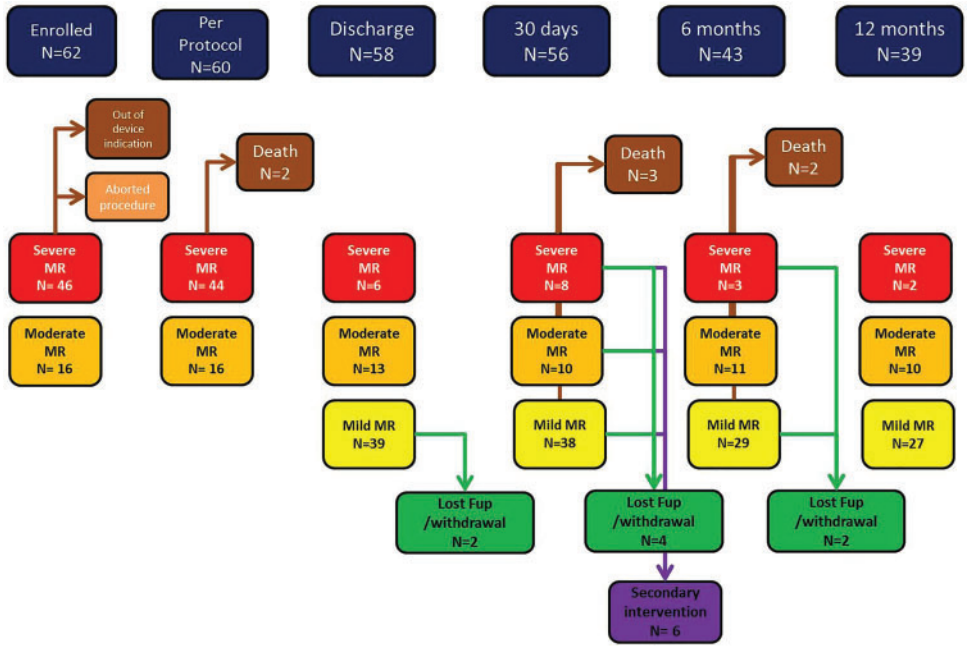


Figure 1 Flow chart presenting the overall population, clinical outcome, degree of mitral regurgitation (MR), and changes over time during follow-up (Fup).

stroke, proper placement, and positioning of the device, freedom from unplanned intervention, absence of structural or technical failure or complications, and MR reduction of at least one MR grade. Procedural success at 30 days was defined as device success without valve-related complication; and absence of death, stroke, myocardial infarction, life-threatening bleeding, major vascular complication, and shock.

Statistics

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as number (percentage). Paired comparison with baseline values were performed using a paired *t*-test or Wilcoxon non-parametric tests. Overall survival and event-free survival were assessed using the Kaplan–Meier analysis. A two-sided *P*-value <0.05 was considered statistically significant. Statistical analysis was conducted using JMP software (SAS Institute).

Results

Population

Sixty-two patients were enrolled in the trial. The procedure was aborted in one patient due to the occurrence of right coronary air embolism, ST elevation, and sustained hypotension immediately after transseptal puncture and before Cardioband implantation. A second patient was excluded from the analysis due to treatment outside of the device indication (unstable clinical condition). This patient, with very severe post-partum cardiomyopathy, was successfully implanted but partial dehiscence led to severe residual MR. The patient's condition deteriorated, and she died despite a left ventricular assist device implantation. Thus, 60 patients who completed the procedure according to the protocol were analysed (*Figure 1*).

The first patient was implanted in February 2013 and the last patient in June 2016. Baseline characteristics of the population are presented in *Table 1*. Mean age was 72 ± 7 years and 43 (72%) were male. Most of the patients were severely symptomatic, and 52 patients (87%) were in NYHA functional Class III or IV. Forty-six patients (77%) had atrial fibrillation and mean ejection fraction was 33 ± 11%. Nineteen patients (32%) had a previous coronary artery bypass graft. Patients were considered at high surgical risk, mean Euroscore I was 18 ± 12% and mean Euroscore II was 7 ± 6%. Mitral regurgitation aetiology was ischaemic in 36 patients (60%) and non-ischaemic in 24 patients (40%). Mitral regurgitation degree was severe in 44 patients (73%) and moderate in 16 patients (27%) (*Figure 1*). PISA quantification was performed in 34 patients; mean ERO was 26 ± 10 mm^2 and mean RVol was 37 ± 14 mL.

Technical, device, and procedural success at 30 days

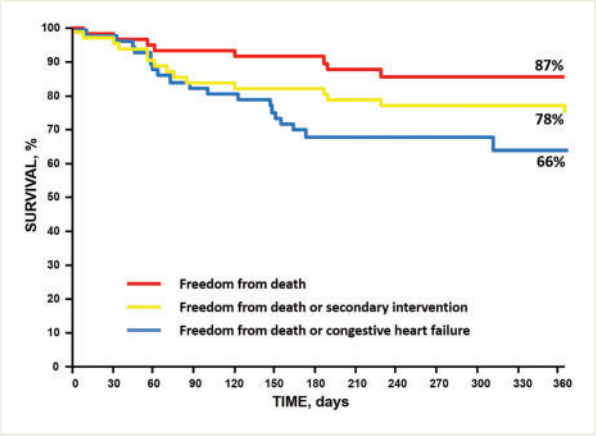
The total procedural time and device implantation time were 201 ± 58 min and 175 ± 50 min, respectively. In one patient, an left atrial appendage (LAA) occlusion was performed during the index procedure. There was no procedural death; however, an implant contraction failure was noted in two patients and was therefore considered device failure. Technical success was 97% (58/60) (95% confidence interval (CI) 89–99).

There was one immediate post-procedural stroke, one myocardial infarction due to a circumflex artery occlusion (due to a device anchor) requiring mechanical support, and one tamponade. One

Table 1 Baseline characteristics ($n = 60$)

Age (years)	72 ± 7 (68–78)
Male	43 (72%)
Diabetes	20 (33%)
Coronary artery bypass graft	19 (32%)
Internal cardioverter defibrillation[a]	18 (33%)
Cardiac resynchronization therapy[a]	11 (20%)
Renal insufficiency	45 (75%)
NYHA functional Class III or IV	52 (87%)
Atrial fibrillation	46 (77%)
Euroscore I[a] (%)	18 ± 12
Euroscore II[a] (%)	7 ± 6
STS score[a] (%)	5 ± 6
Ischaemic aetiology of regurgitation	36 (60%)
Severe mitral regurgitation	44 (73%)
Moderate mitral regurgitation	16 (27%)
Effective regurgitant orifice (mm^2)	26 ± 10
Regurgitant volume (mL)	39 ± 14
Ejection fraction (%)	33 ± 11
Systolic pulmonary pressure (mmHg)	37 ± 11

Values are mean ± SD or number of patients (percentage).
[a]Data not available for five patients.



Take home figure Event-free survival curves at 1 year for freedom from death, freedom from death or secondary intervention, and freedom from death or congestive heart failure.

patient also experienced a cardiac arrest due to ventricular rhythm disturbance related to a distal circumflex obstruction. In addition, anchor disengagement was observed in 10 patients (all but 1 in the first 28 patients) resulting in device inefficacy in 5 patients. There was no device migration or embolization as a result of anchor disengagement, and all device dehiscence were partial. No device dehiscence led to intravascular haemolysis. There was a significant reduction of the septolateral diameter as measured by echocardiography (3.7 ± 0.4 vs. 2.6 ± 0.4 cm, $P < 0.01$), and MR grade improved by at least one grade in all but eight patients. Importantly there was no occurrence of mitral stenosis. According to MVARC definition—acceptable—device success was 72% (43/60) (95% CI 59–81).

During the index hospitalization there were two deaths, none device or procedure-related. One patient died a few days after device implantation of a haemorrhagic stroke while being treated by aspirin, ticagrelor, heparin, and vitamin K antagonist before MR severity could be assessed. The second patient who underwent a successful device implantation but a secondary dehiscence leading to severe MR recurrence and congestive heart failure was operated on and died 4 weeks post-operatively. There was one cardiogenic shock requiring inotropic support due to severe left ventricular dysfunction and two episodes of congestive heart failure. The procedural success was 68% (41/60) (95% CI 56–79).

Clinical outcomes at 1 year

Fifty-eight patients left the hospital alive. Due to loss of follow-up or consent withdrawal, clinical and echocardiographic evaluation could not be performed in eight patients (two patients after discharge, four patients after 30 days, and two patients after 6 months), and these patients were censored at the date of their last visit. After 30 days, there were five additional deaths (three cardiac and two non-cardiac deaths). Mitral regurgitation grade at the previous visit for these five patients was severe in one patient, moderate in two patients, and mild in two other patients. Survival at 1 year was therefore 87% (95% CI 75–94) (*Take home figure*). Sixteen patients were also readmitted within the first year for congestive failure including two patients who eventually died. Six patients underwent a secondary transcatheter mitral procedure with another device for recurrent/persistent significant MR, and these patients were censored at the time of the secondary procedure. Survival rates free of readmission for heart failure and survival free of secondary procedure at 1-year were 66% (95% CI 52–77) and 78% (95% CI 67–88%), respectively. In addition, two patients underwent an atrial septal closure, one for persistent hypoxaemia and one for severe right chamber enlargement. One patient experienced late mitral valve infective endocarditis.

Device efficacy and mitral regurgitation recurrence

At the latest in-hospital echocardiographic evaluation (available for all but one patient), 7 patients (12%) had severe MR (including the patient who was operated on and eventually died), 13 patients (22%) had moderate MR, and 39 patients (65%) had mild or less MR. Between discharge and 30-day evaluation (performed in 56 patients due to the two deaths and 2 patients who were lost to follow-up or withdrew consent), the MR grade improved in 5 patients (from moderate to mild) and worsened in 6 patients (2 from moderate to severe and 4 from mild to moderate). Mitral regurgitation grade at 6 months (assessed in 43 patients) and at 12 months (assessed in 39 patients) was mild in 67% and 69%, respectively and moderate in 26% at both time points (*Figures 1* and *2*). Considering the overall cohort ($n = 60$) including patients who died, were lost to follow-up, withdrew consent, or underwent a secondary procedure, 66% and 61% of the cohort presented with moderate or less MR grade at 6 and 12 months, respectively (*Figure 3*). Among the 51 patients in which the procedure was considered successful in terms of MR reduction at discharge, MR recurrence (increase of at least one grade) over

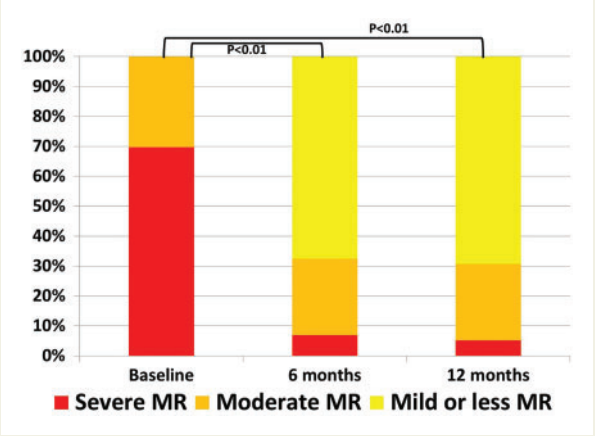


Figure 2 Paired comparisons of the severity of the mitral regurgitation at 6 months ($n = 43$) and at 12 months ($n = 39$) compared to baseline.

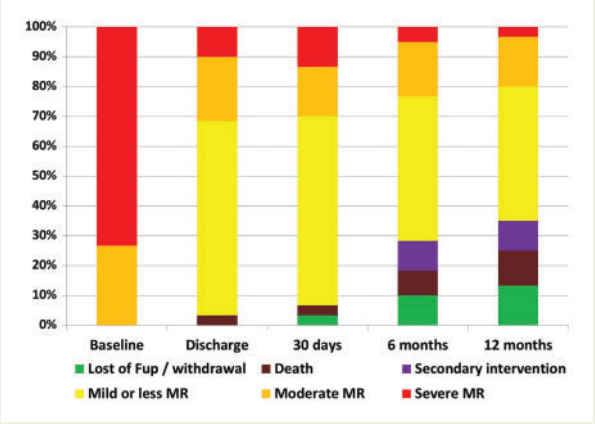


Figure 3 Bar graph representing the percent of the population ($n = 60$) according to degree of mitral regurgitation, death status, and performance of secondary intervention over time.

time was observed in 6 patients (12%) at 30 days, in 11 patients (22%) at 6 months and 11 patients (22%) at 12 months, cumulatively. Among the 16 patients with moderate MR at baseline, only one didn't improved at 30 days but later improved at 6 and 12 months and 3 other patients worsened from mild to moderate at 12 months.

Septolateral diameter reduction was sustained after discharge in the patients evaluated at 6 and 12 months (2.5 ± 0.5 cm and 2.5 ± 0.4 cm vs. 2.6 ± 0.4 respectively, both $P > 0.40$).

Functional evaluation

NYHA functional class was assessed in 42 patients at 6 and 12 months. Compared to baseline, a significant improvement was observed; 35 patients (83%) and 33 patients (79%) at 6 and 12 months respectively, were in NYHA Class I/II compared to only 14% at baseline ($P < 0.01$). The 6MWT was performed at 6 and 12 months in 38 and 32 patients, respectively. Clinically and statistically significant improvements were observed compared to baseline (342 ± 129 m at 6 months vs. 285 ± 123 m at baseline, +57 m improvement $P < 0.01$ and 367 ± 144 m at 12 months vs. 309 ± 123 m at baseline, +58 m improvement $P < 0.01$). The Minnesota Living with Heart Failure score significantly improved by 19 and 20 points at 6 months and 12 months, respectively (19 ± 14 at 6 months vs. 39 ± 19 at baseline (measured in 41 patients) and 20 ± 18 at 12 months vs. 39 ± 20 at baseline (measured in 39 patients), both $P < 0.01$).

Discussion

In this study, the Cardioband system showed a satisfactory safety profile, provided significant MR reduction in most of the patients, and was associated with significant functional improvements.

This is the largest series reporting both the immediate and mid-term outcome of consecutive patients who underwent the Cardioband procedure from the early initial experience.[12,16,17] Based on the satisfactory device safety, the device obtained the Conformité Européene (CE Mark) approval in September 2015. Two cases of circumflex artery injury occurred. This is a well-known complication of mitral valve surgery. Since then, the screening process has improved based on CT evaluation, and a procedural coronary angiography is recommended before inserting and releasing anchors, especially for the first anchors due to the close proximity of the circumflex artery to the mitral annulus near the lateral commissure.

As with all new devices, technical/device failures are to be expected in the early phase of clinical experience. Anchor disengagement was observed in the early phase of the study (9 of the 10 anchor disengagement occurred in the first 28 patients enrolled). Importantly, anchor disengagement resulted in only partial device detachment which may have impacted device efficacy but there was no device migration or embolization. Since anchors are delivered through the sleeve, if disengaged, they remain within the band and there is theoretically no risk of anchor migration or embolization. It is worth noting that all incidents of anchor disengagement were immediate and therefore attributed to improper or insufficient anchor insertion. No late disengagement was reported. Significant improvements were implemented to address these issues. First, anchor length was increased from 4 to 6 mm to ensure better anchoring within the tissue. Second, the lateral commissure area provides important support during reduction, and this area was reinforced by increasing the number of anchors inserted from 2 to 3. The P2 area was the second area at risk for disengagement and improvement in imaging of this area using multiple views and careful attention during the pull test led to a marked reduction of these incidents. In addition, device design was improved to avoid contraction failure which also occurred early in the series. Finally, as expected for a new device there is a learning curve. Training of both interventional cardiologists and echocardiographers is crucial, and the standardization and reproducibility of the procedure has improved over time. A reduction of procedural and implantation times is expected to occur with experience and standardization as with other devices.

The cardioband device led to a marked reduction in MR, and 95% of the evaluable patients at 1 year presented with moderate or less MR. Significant and sustained reduction of the mitral annulus diameter

was also observed as well as significant functional improvement using multi-parameter assessment. The concordance of improvements in NYHA class, 6MWT, and MLHFQ score is reassuring. It is also worth noting that despite our population presented with a high-risk profile, the observed one year mortality was approximately half the one usually observed in such population.

Comparing performance with other devices is not easy. First, grading of MR severity and definitions of device success are variable and populations are often a mix of primary and secondary MR. For instance, the good results observed with the Mitraclip® should take into account the that the definition of procedural success was different (defined as a composite of post-implantation MR of grade ≤ 2, without conversion to open cardiac surgery, and without in-hospital mortality).[18] Second, only paired comparisons are usually presented which tend to overestimate the device efficacy as patients who died or underwent a surgery/secondary intervention are excluded from such analyses yet are more likely to present unsatisfactory results. In the present study, we report both paired and overall results taking into account death and secondary intervention. In addition, the true magnitude of the device effect is somewhat confounded and reduced by the inclusion of the first-generation device and the presence of a learning curve. Procedural success rates with the MitraClip have thus improved since the early phase.[18] Nevertheless and despite all the limitations mentioned above, the Cardioband system results are in line with those of the MitraClip at its early phase and better than those currently reported with Carillon or Mitralign.[19–21]

Some degree of MR recurrence was observed which is to be expected and perhaps unavoidable for patients with secondary MR. Secondary MR is a consequence of left ventricular remodelling and conformational changes of the mitral valve apparatus and is typically assessed based on tenting area.[22] Mitral annulus dilatation is almost constantly observed but is not the leading mechanism of secondary MR. Surgical series have shown that up to one-third of patients with secondary MR experienced significant MR recurrence 1 year after surgical annuloplasty.[11] This point raises three important considerations. First, unlike surgical annuloplasty and current percutaneous repair devices, the Cardioband system is adjustable and can be tailored under beating heart conditions to meet individual patient needs. Second, the Cardioband implant does not preclude the use of a secondary intervention such as leaflet repair, as shown in this series with six patients who underwent a secondary intervention. A fully percutaneous annular and valvular correction is very attractive and promising for both secondary and primary MR. Third, the mitral valve apparatus is much more complex than the aortic valve. The importance of the tenting and of the posterior leaflet restriction is highly variable across patients with secondary MR. According to a comprehensive analysis of mitral valve anatomy and function, a personalized percutaneous transcatheter approach might be proposed. In a near future, transcatheter mitral valve replacement may be preferred in patients with excessing tenting or very restrictive posterior leaflet while a percutaneous annuloplasty may be proposed first in the absence of these conditions followed by a leaflet procedure if needed.

Our study deserves several comments. First, it was a multicentre study with a relatively small sample size (although the largest to date). Second, as mentioned earlier, significant device and procedural modifications were introduced during the course of the study and the skills of the operators improved over time. Third, quantitative assessment of MR was performed in a subset of the patients during follow-up. However, all assessments were performed by a centralized and independent core lab using an integrative approach as recommended by the current guidelines. Fourth, definition of optimal cinching was subjective and relied on semi-quantitative assessment of both MR degree and leaflets tethering/restrictive mobility. Standardization will improve reproducibility and diffusion of the technique. In addition, MR assessment was performed under general anaesthesia and normal haemodynamic conditions. Usefulness of stimulation tests in this setting deserves further evaluation. Fifth, minor differences with previous publications were observed that are related to differences in sample size, definitions of endpoints and timing. Importantly, we currently provide a clear evaluation of the rate of anchors disengagement which although mentioned was not reported in a systematic manner. Finally, this was a single-arm study, and there was no control group; therefore, clinical efficacy and MR reduction could only be compared to baseline. Further studies are warranted and the randomized controlled ACTIVE Trial (NCT03016975), evaluating the Cardioband system in conjunction with guideline-directed medical therapy compared to guideline-directed medical therapy alone, is currently underway in the USA.

Conclusion

In the present study, we report the immediate and 1-year results of the consecutive cohort of patients who underwent the Cardioband customized annular reduction procedure that led to the CE approval of the device. A reasonable performance and safety were demonstrated. At 1-year, MR severity was moderate or less in most patients and significant functional improvement was observed although one-fifth of the patients experienced MR worsening by at least one grade. In addition, the Cardioband procedure did not preclude a secondary transcatheter mitral procedure. The ACTIVE randomized trial is underway to confirm these early promising results.

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Conflict of interest: D.M.-Z. is a consultant for Edwards Lifesciences, Mardil and Cardiawave and receives research grants from Edwards Lifesciences and Abbott vascular. G.N: none. A.L. is consultant Abbott Vascular, Medtronic and Mitraltech and receives research grants from Abbott Vascular, Medtronic, Edwards Lifesciences and Mitraltech. K.-H. K. is consultant for St. Jude Medical, Abbott Vascular and Medtronic. S.B., R.S. , and G.L.C. none. E.A.: honoraria from Edwards Lifesciences. F.K. is consultant for Edwards LifeSciences, Abbott and Cardiac Implants. M.H.: none. M.Z. is a proctor for Valtech. P.V. is an Edwards Lifesciences employee. P.G. reports grants from ValTech Cardio (now Edwards Lifesciences), during the conduct of the study; grants and personal fees from Abbott Vascular, grants and personal fees from Edwards

Lifesciences, grants and personal fees from Medtronic, other from Neochord, outside the submitted work. A.V. is consultant for Edwards Lifesciences, Abbott vascular and Mitraltech. F.M. is consultant Edwards Lifesciences and has financial interest in Valtechcardio and Edwards Lifesciences.

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