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FASTTRACK CLINICAL RESEARCH
Valvular heart disease

Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial

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Aims Cardioband system is a direct annuloplasty adjustable device that is implanted in the beating heart on the posterior annulus under fluoroscopic and transoesophageal echocardiographic (TEE) guidance. We report the early (1 month) outcomes of the first-in-man pre-CE-mark feasibility and safety trial.

Methods and results The study enrolled high-risk adult individuals at five institutions in Europe with symptomatic secondary mitral regurgitation (MR) despite optimal medical therapy. The primary efficacy endpoints included the technical success rate of implantation, feasibility of the Cardioband adjustment (technical performance), and ability to reduce the annular septolateral dimension and MR grade at hospital discharge and at 30 days. The study group included 31 consecutively enrolled high-risk patients with moderate-to-severe or severe secondary MR with at least 1 month of follow-up (mean age 71.8 $\pm$ 6.9 years). All patients received the full implant of a Cardioband. Adjustment of the Cardioband resulted in a significant reduction in the septolateral dimension in all but two patients (septolateral dimension from 36.8 $\pm$ 4.8 to 29 $\pm$ 5.5 mm after the procedure, $P < 0.01$). Following Cardioband adjustment (29 of 31 patients) MR was none or trace in 6 (21%), mild in 21 (72%), and moderate in 2 (7%). No patient had severe MR after adjustment. Procedural mortality was zero and in-hospital mortality was 6.5% (2 of 31 patients, neither procedure- nor device-related). At 30 days, 22 of the 25 patients (88%) had MR $\leq$2+.

Conclusions This study demonstrates the feasibility and safety of percutaneous direct mitral annuloplasty with the Cardioband device in high-risk patients with MR.

Keywords Transcatheter mitral repair • Direct annuloplasty • Secondary mitral regurgitation

Introduction

Transcatheter mitral valve interventions are progressively being introduced into clinical practice targeting a population of patients with mitral regurgitation (MR) deemed inoperable or at an unacceptable surgical risk.[1] Although MitraClip (Abbott Vascular, Santa Rosa, CA, USA) therapy is widely performed, there are presently no direct percutaneous annuloplasty devices available for clinical use. Annuloplasty in an open-chest surgical approach is the most commonly performed repair treatment for MR. Annuloplasty is added to leaflet repair in degenerative MR to improve coaptation and prolong durability, and it is often used as a stand-alone procedure to improve

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coaptation in secondary MR (MR), also referred to as functional MR (FMR). Secondary MR is caused by sustained previous damage to the left ventricle due to a myocardial infarction or dilated cardiomyopathy, resulting in annular dilatation and lateral displacement of the papillary muscles.

The Cardioband system (Valtech Cardio, OrYehuda, Israel) is a percutaneous surgical-like direct annuloplasty device that is implanted in the beating heart on the posterior annulus under fluoroscopic and transoesophageal echocardiographic (TEE) guidance. Following the implantation, it is contracted to remodel the annulus and improve MR. We report the early (1 month) outcomes of the first-in-man pre-CE-mark feasibility and safety trial. The study outcomes represent the early experience of five European sites.

Methods

Trial design, inclusion criteria, and patient selection

The study was a non-blinded, non-randomized, single-arm, multicentre, prospective study enrolling patients from five institutions in Europe. The study enrolled high-risk adult individuals with symptomatic MR despite optimal medical therapy including cardiac resynchronization therapy (CRT) where indicated. Patients with a left ventricular (LV) ejection fraction $\leq$25% and an LV end-diastolic diameter $\geq$70 mm were excluded. Other main exclusion criteria are organic lesions of the mitral valve, calcification of the annulus, acute endocarditis, coronary artery disease requiring revascularization, dialysis, significant concomitant valve disease, life expectancy $<$12 months, and recent cerebral event.

All the patients underwent preprocedural TEE and cardiac computed tomography (CT) to assess anatomical feasibility. Computed tomography scanning was used to size the mitral annulus, and to plan the procedure (location of transseptal puncture, mitigating the risk of injury to the left circumflex coronary artery, and planning of fluoroscopic views).

The implant size was chosen according to the length of the posterior annulus (from left trigone to right trigone) at maximal diastolic opening of the valve.

The primary efficacy endpoints included:

(a) Technical success rate of Cardioband implantation, defined as the ability to advance the implant, load anchors, anchor the implant to the tissue, and retract the implant delivery system;
(b) Technical feasibility of Cardioband adjustment, defined as the ability to connect the adjustment tool, reduce the implant dimension, and retract the adjustment tool with the guide wire;
(c) Cardioband ability to reduce the annular septolateral dimension and MR as measured by TEE post-procedure, and transthoracic echocardiography (TTE) at hospital discharge and at the post-operative 30-day visit.

The standardization of echocardiographic images was achieved by using a pre-specified protocol that addressed the issues of echocardiographic acquisition. Mitral regurgitation was assessed by an independent Core-Laboratory. Mitral regurgitation severity is determined by a combination of qualitative and quantitative methods as per the Echocardiography Society guidelines for MR analysis in MR patients.[2] Analysis of echocardiography data was performed both by the investigational site and in a standardized mode by an independent core laboratory (Paul Grayburn, MD, Baylor Health, TX, USA).

The overall rate of major serious adverse events (MSAEs) and serious adverse device effects (SADEs) until hospital discharge and at 30 days post implantation was the primary safety endpoint. Both the MSAEs and the SADEs were collected and independently adjudicated by a Clinical Event Committee. Major serious adverse events include death, myocardial infarction, cardiac tamponade, device-related cardiac surgery, and stroke.

The clinical investigation was performed in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice (GCP) principles, and in accordance with ISO 14155:2011. The study has been registered at ClinicalTrials.gov as NCT01841554.

The Cardioband adjustable annuloplasty system

The Cardioband adjustable annuloplasty system includes the implant and three main accessories:

(a) *The implant* is a polyester sleeve with radiopaque markers spaced 8 mm apart (*Figure 1A* and *B*). The sleeve mounted on the delivery system and the anchor deployed from the internal part. A contraction wire in the Cardioband is connected to an adjusting spool. Activating the spool enables shorten the implant. The implant size is adjusted to the patient's needs under TEE guidance and the size can be completely reversed. The implant is available in six lengths (*Table 1*).
(b) *TF Delivery system*: The Cardioband delivery system (CDS) consists of the implant delivery system (IDS) and the 25F transseptal steerable sheath (TSS). The IDS comprises a steerable guide catheter (GC) and an implant catheter (IC) with the Cardioband implant mounted on its distal end (*Figure 1C*).
(c) *Implantable metal anchors and anchor delivery shafts:* Implantable stainless steel, 6 mm long anchors, is used to fasten the Cardioband implant to the annulus (*Figure 2*). Between 12 and 17 anchors are implanted using a delivery shaft. The anchors are fully repositionable and retrievable until deployed.
(d) *Size adjustment tool* (SAT): The SAT distal tip is connected over the implant wire and is used to control the implant adjustment spool and the implant size.

The procedure

The procedure is performed under general anaesthesia with 3D TEE guidance. Femoral vein and arterial access is obtained. Following echo-guided transseptal puncture, systemic heparinization is performed to achieve an activated clotting time between 250 and 300 s. The TSS is advanced over a super-stiff guide wire into the left atrium. The IDS is then advanced through the TSS. The delivery system is steered, until the tip of the IC is placed over the anterior commissure. Verification of the first anchoring location is obtained with TEE. The anchor should be placed close to the leaflet hinge, as anterior as possible in the annulus, close to the anterior commissure. Following confirmation of the location with 3D TEE, coronary angiography is performed to rule out the risk of circumflex damage. The first anchor is delivered and implanted using the anchor delivery drive inside the IC through the Cardioband implant fabric and into the annulus tissue. The anchor is released after proper anchoring is checked with push-and-pull testing under echocardiographic and standardized fluoroscopic guidance. The Cardioband implant is deployed until the radiopaque marker of the IC channel reaches the next marker on the implant. The IC tip is then navigated, by actuating the TSS and GC steering knobs, to the next anchoring point along the posterior annulus using echocardiographic guidance. These actions are repeated until the implant catheter tip reaches the last anchoring site on the posterior commissure.

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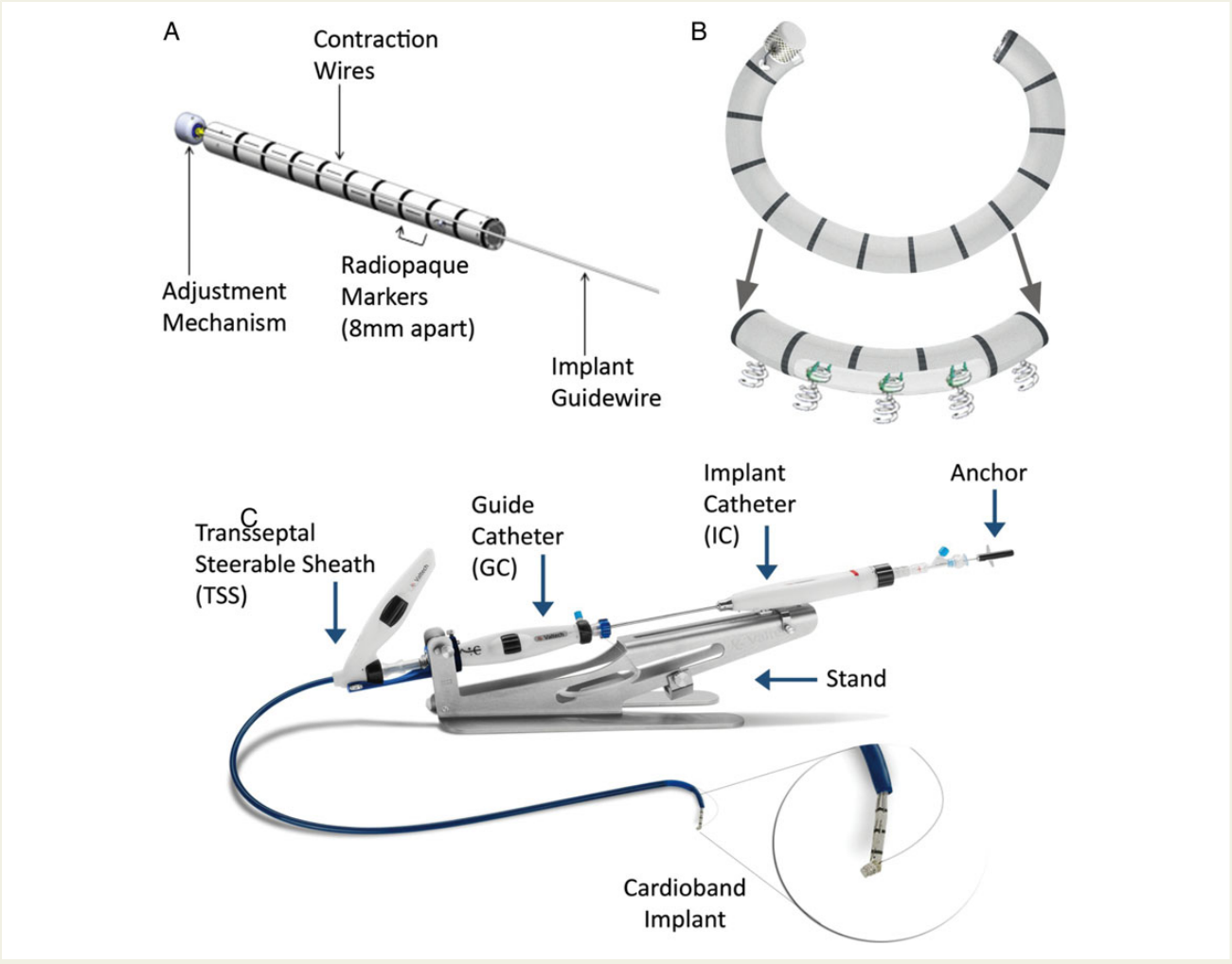


Figure 1 Cardioband implant before implantation (*A*) and after implantation (*B*). The implant is a polyester sleeve with radiopaque markers spaced 8 mm apart. (*C*) The Cardioband delivery system, assembled in the implantation mode. The Cardioband delivery system consists of an implant delivery system and a 25F transseptal steerable sheath. The implant delivery system comprises a steerable guide catheter and an implant catheter with the Cardioband implant mounted on its distal end.

Table 1 Cardioband implant size (*N* = 31)

Implant size	No. of subjects (%)
B (81–88 mm)	1 (3)
C (89–96 mm)	5 (16)
D (97–104 mm)	13 (42)
E (105–112 mm)	7 (23)
F (113–120 mm)	5 (16)

The last anchor is then deployed and the implant disconnected from the IDS is subsequently removed. The SAT is then inserted through the TSS, over the implant guide wire, until its distal end reaches the adjustment spool of the implant. After SAT connection, the implant is contracted by clockwise rotation of the adjustment roller (*Figure 3*). Adequate reduction of MR severity is assessed by TEE under beating-heart conditions. When the appropriate implant size has been reached, the SAT is detached from the adjustment spool leaving the implant with the desired degree of contraction.

Statistics

Statistical analysis was conducted using JMP 8.0 software (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as mean ± SD or as median (IQR, Q1–Q3) and categorical variables are expressed as percentages. Univariable comparisons (differences between pre- and post-values) were performed with the Student's paired *t*-test for continuous normally distributed data, which was tested by the Shapiro–Wilk normality test. A *P*-value of <0.05 was considered statistically significant; reported *P*-values are two-sided. The two-sided 95% confidence interval (CI) of clinical prevalence was calculated using the Clopper–Pearson method.

Results

Patients

On 31 January 2015 consecutively enrolled patients with secondary (functional) MR had reached at least 1 month of follow-up. The

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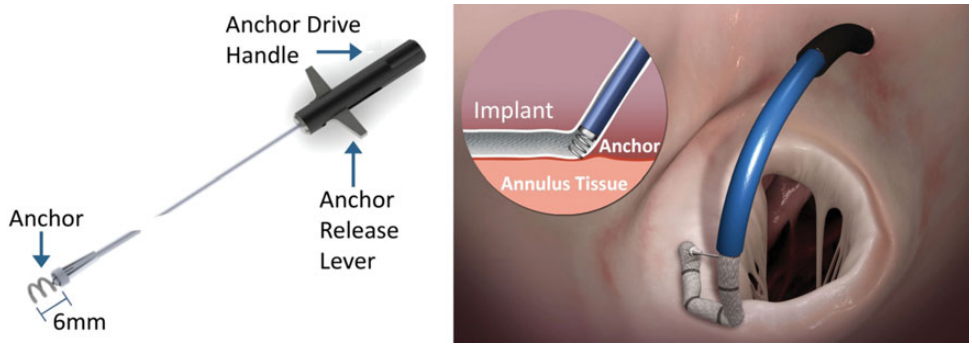


Figure 2 Anchor delivery system and implantable metal anchor (left panel). Anchor deployment through implant and tissue (right panel). The anchor is delivered and implanted using the anchor delivery drive inside the implant catheter through the Cardioband implant fabric and into the annulus tissue under echocardiographic and standardized fluoroscopic guidance.

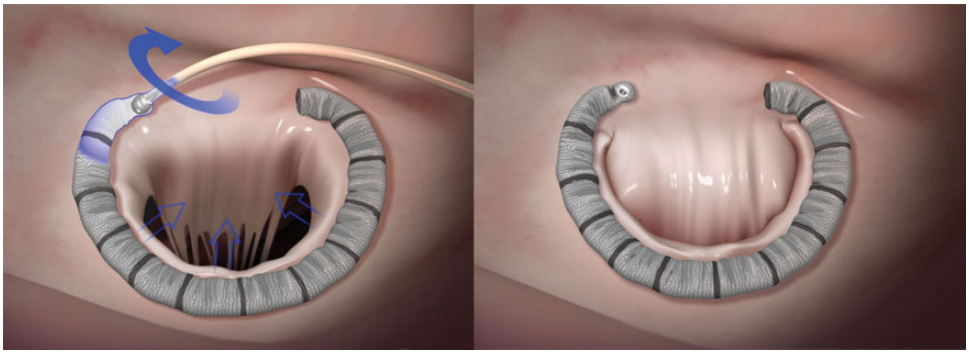


Figure 3 Cardioband adjustment. The size adjustment tool distal tip is connected over the implant wire and is used to control the implant adjustment spool. Activating the spool shortens the implant. The implant size is adjusted to the patient's needs under transoesophageal echocardiographic guidance.

majority of patients (19/31 [61%]) had restricted leaflet motion (Carpentier classification type IIIb), while the remaining had predominantly annular dilatation (Type I MR). Aetiology of secondary MR was ischaemic in 60% of the patients. Mean age of the patients was 71.8 ± 6.9 years, and 26 patients (84%) were male. All patients were symptomatic for congestive heart failure after optimization of medical therapy and CRT where indicated; 30/31 patients were in NYHA functional class III–IV.

Coronary artery disease was the identifiable cause of heart failure in 18 patients (58%), and 10 patients (32%) had a history of myocardial infarction. Fourteen patients (45%) had previously undergone open-heart surgery at least once. Most common comorbidities included moderate to severe renal impairment (92%), atrial fibrillation (77%) diabetes (45%), poor mobility (23%), chronic pulmonary disease (23%), prior stroke (12%), extracardiac arteriopathy (10%), and neurological dysfunction (3%).

According to the core-lab adjudication at the time of pre-procedural screening, MR was moderate to severe in all patients, with no patient showing organic leaflet motion abnormalities, as per protocol. Average LV ejection fraction, LV end-diastolic volume, and LV end-systolic volume were 34 ± 11%, 188 ± 51, and 127 ± 49 ml, respectively. Moderate to severe pulmonary hypertension was present in 22 patients (71%). Concomitant moderate to severe tricuspid regurgitation was present in 14 patients (45%).

Procedural outcomes

Technical implantation success rate

All patients in whom the procedure was initiated received the full implant of a Cardioband. However, the technical success rate of implantation was 93.6% (CI: 78.6–99.2%), because in one case, two anchors were not implanted and the implant did not reach the posterior commissure, due to technical difficulties in the early phase of the experience. In another case, the implant size could not be reduced due to technical failure. According to the pre-procedural CT scan, most patients (13/31 [42%]) had a posterior annular size between 97 and 104 mm.

The total procedure duration was 3:06 ± 0:46 h, while the average implantation time (2:45 ± 0:44) tended to become shorter with growing operator experience (*Figure 4*).

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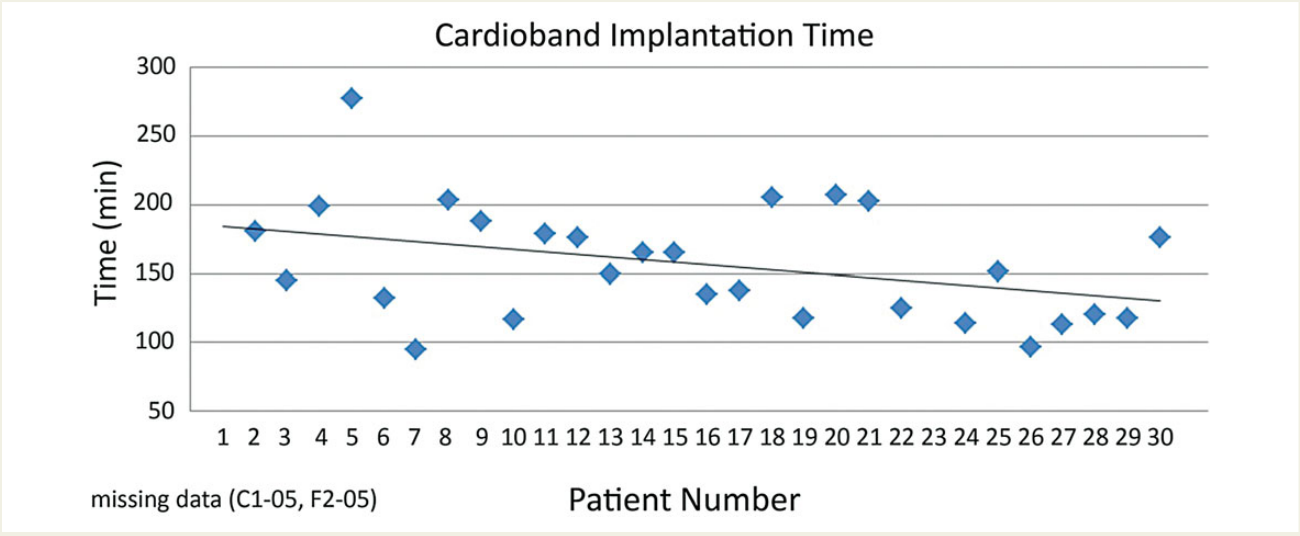


Figure 4 Duration of Cardioband implantation over time for the first 30 patients. The average implantation time (2:45 ± 0:44) tended to become shorter with growing operator experience.

Technical adjustment success rate

The technical performance of Cardioband adjustment was fully successful in 29 of 31 subjects (93.6%; CI: 78.6–99.2%). Connecting the adjustment tool was fully successful in 31/31 subjects (100%), reducing the septolateral dimension was fully successful in 30/31 subjects (96.8%), and retracting the adjustment tool with the guide wire was fully successful in 29/31 subjects (93.6%). Failures were due to device malfunction and procedural errors which occurred early in the series and which have been identified and solved.

Adjustment of the Cardioband device resulted in a significant reduction in the septolateral dimension in all study patients but two. The average septolateral dimension was 36.8 ± 4.8 mm before the procedure and 29.0 ± 5.5 mm after the procedure, resulting in a significant overall reduction of 21.1% ($P < 0.0001$) (*Figure 5*).

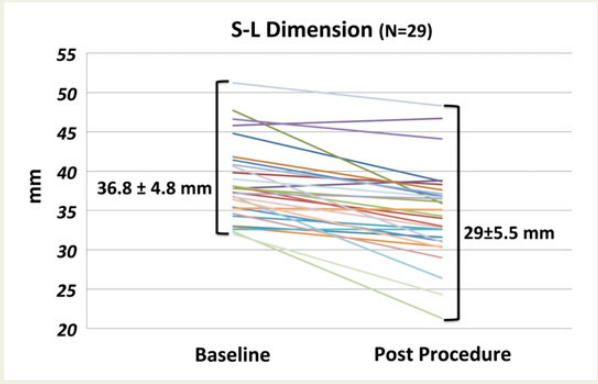


Figure 5 Septolateral dimension (in mm) at baseline and post Cardioband procedure for the first 31 patients.

Intra-procedural mitral regurgitation reduction

Intraoperative MR (TEE) following Cardioband adjustment (available in 29 patients) was none or trace in 6 (21%), mild in 21 (72%) and moderate in 2 (7%). No patient had severe MR after Cardioband adjustment. At 30 days (core-lab adjudication data available for 27 patients), MR was uncertain in 2 (7%), none or trace (<1+) in 1 (4%), mild (1+) in 17 (63%), moderate (2+) in 4 (15%), and severe (3+/4+) in 3 (11%). Thus, 22 (88.0%; CI: 68.8–97.5%) of 25 patients had MR ≤2+ at 30 days (*Figure 6*). Effective Regurgitant Orifice Area decreased from 0.28 ± 0.11 cm^2 at baseline to 0.17 ± 0.13 cm^2 at 30 days ($P = 0.04$).

Safety

Procedural mortality was zero, in-hospital mortality was 6.5% (2/31 patients; CI: 0.79–21.4%), one patient died as a result of haemorrhagic stroke and another patient died of multi-organ failure 30 days after elective open-heart surgery. The first event was a complication of a triple anticoagulant therapy that was indicated because of a recently implanted stent and atrial fibrillation. This therapy was the same as before the Cardioband procedure, and therefore, it was concluded that this event was unrelated to the device or procedure. The second fatal event was due to an elective surgical mitral valve replacement and tricuspid annuloplasty procedure following unsatisfactory MR reduction due to inability to adjust the annular dimension (device malfunction). This event was not related to the device or procedure, since the decision to perform the mitral valve surgery was unrelated to the Cardioband implantation and the subsequent device malfunction. Overall, 16 serious adverse events (SAEs) were reported in 9 patients until 30 days post implantation. All SAEs were expected. The 16 SAE's were as follows: 2 fatal events (1 of which haemorrhagic stroke), 2 MR recurrence (related to device, partial anchor detachment at early phases), 2 renal insufficiency (possibly related to procedure), 2 pericardial effusion (possibly related to procedure), 1 open-heart surgery, 1 left femoral pseudo aneurysm (related to procedure), 1 bleeding complication (related to

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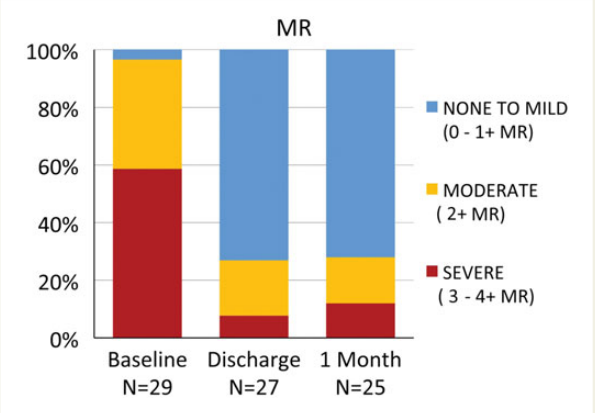


Figure 6 Mitral regurgitation reduction by transoesophageal echocardiography at baseline ($N = 29$) discharge ($N = 27$) and 1-month follow-up ($N = 25$) for the first 31 patients (core-lab assessment). Twenty-seven patients were analysed at discharge; two patients died prior to discharge and the echo results were uncertain by core-lab for two patients. Twenty-five of the 31 patients were analysed at 1-month follow-up two died prior to discharge, one withdrew prior to 1-month follow-up, the echo results were uncertain for two patients. One patient had mild MR measured by transoesophageal echocardiography at baseline, but had moderate mitral regurgitation as determined by transoesophageal echocardiography and was therefore included in the study.

procedure), 1 dyspnoea, 1 upper limb hemiparesis, 1 gastrointestinal bleeding, 1 prolonged hospitalization for diabetes management, and 1 hospitalization to treat a home accident.

Discussion

The initial experience with the Cardioband system shows that transfemoral implantation of a surgical-like direct annuloplasty device is feasible, safe, and effective. Cardioband device closely reproduces surgical annuloplasty with sustained and effective septolateral reduction of the annulus and MR reduction in all patients.

Annuloplasty to treat mitral regurgitation

Isolated transcatheter direct annuloplasty may play a major role in the treatment of patients with MR deemed inoperable or at high surgical risk. Patients with LV dysfunction and significant MR have a poor prognosis and increasing severity of MR is associated with the worse outcome.[3] Although a survival benefit has not yet been clearly demonstrated, surgical repair of severe FMR has been associated with improvement of symptoms and quality of life and with reverse LV remodelling.[4,5] Surgical correction of MR is mainly performed by way of an undersized annuloplasty[6,7]: by reducing the septolateral dimension of the mitral annulus, undersized annuloplasty forces leaflets coaptation, and thereby reduces MR. However, perioperative mortality after mitral surgery for MR is not negligible, ranging from 8.8 to 21% in different series,[5,8–10] and the number of patients with severe MR who are not referred for surgery is increasing.[11]

Percutaneous annuloplasty

The less invasive, percutaneous implantation of a 'surgical-like' annuloplasty device offers the opportunity of safer treatment when compared with conventional open-heart surgery. It may also have a potential role in an earlier indication for treatment to improve the chance of prognostic benefit.[12] Multiple transcatheter technologies and various approaches are presently under clinical study or in development.[1] To date, Cardioband is the only device that closely reproduces surgical annuloplasty with a transcatheter approach. After demonstrating the proof of concept and feasibility in a chronic animal model,[13] the Cardioband device was initially implanted in humans under direct vision through right mini thoracotomy.[14] Initial experience in five patients with degenerative MR who underwent minimally invasive surgical mitral valve repair showed the feasibility and durability out to 2 years of implantation of the sutureless Cardioband system. This preliminary experience also showed the efficacy of Cardioband adjustability to decrease the septolateral dimension and increase leaflet coaptation. Following this initial clinical experience, the first-in-man fully percutaneous transfemoral implantation was successfully performed in 2013.[15]

Feasibility of Cardioband implantation

The Cardioband device was successfully implanted in all enrolled patients with no intra-procedural mortality. In the EVEREST I trial, MitraClip was successfully implanted in 24 of 27 patients (89%).[16] In the TITAN trial, the procedural success rate of coronary sinus annuloplasty with the Carillon device was only 68% (36 of 53 patients) in the intention-to-treat series,[17] mainly due to anatomical reasons. Even if the patients enrolled in this study were carefully selected, the 100% implantation feasibility of the Cardioband suggests that this device has the potential of wide clinical application in the real world. Compared with MitraClip therapy, Cardioband closely reproduces surgical standard therapy for FMR, and leaves the door open to potential further transcatheter treatments, including mitral replacement.

The learning curve is one of the most important determinants of procedure duration, as previously demonstrated with the MitraClip.[18] Improvement in procedural imaging guidance is expected to shorten the learning period and, thus, procedure duration.

Patient selection, procedural planning, and imaging guidance

The use of CT angiography to plan the procedure was previously validated in an animal study.[19] Pre-procedural CT angiography supports patient selection (next to TEE) and procedural planning, allows the operator to rule out annular calcifications (which represent the most important anatomical contraindication to annuloplasty implantation), size the length of the posterior mitral annulus, plan the correct location for transseptal puncture, and assess the distance between the annulus and the left circumflex coronary artery to estimate the risk of injury. Moreover, CT angiography predicted the optimal fluoroscopic planes to implant the anchors during the procedure.

As for all types of transcatheter mitral valve therapy, advanced integrated imaging played a fundamental role also in procedural

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guidance (3D and 2D TEE live guidance and fluoroscopy) in all steps of the procedure, from transseptal puncture to anchor implantation to final adjustment.

Safety

The safety profile of the Cardioband system is on the order of magnitude of that observed with the MitraClip in real-world clinical use. Intra-procedural mortality was 0%, while 2 of 31 patients (6.5%) died at 30 days/prior to discharge, both not device-related; 30-day mortality in the ACCESS-EU and EVEREST II high-risk registries was 3.4 and 4.8%, respectively.[20,21] The safety of the procedure is also supported by the very low incidence of procedural and device-related major events (only two events). The high safety profile of the procedure is particularly relevant when compared with transcatheter mitral valve replacement, which, although clinical evidence is still very limited, seems to be associated with relatively higher morbidity and mortality in high-risk patients.[1]

Efficacy

The preliminary results obtained with the Cardioband system are comparable with those reported from the EVEREST I study[16] even accounting for a per-protocol analysis. Among the patients who were discharged with at least one successfully implanted clip (24 out of 27 patients), only 64% of the patients had MR $\leq 2+$ at 30 days (compared with more than 80% obtained with the Cardioband device). In the two cases with residual significant MR intra-procedurally, this was related to impossibility to contract the Cardioband after the implantation because of a technical device failure. This device-related failure was solved with an iteration of the device after the first 10 patients and final contraction was successfully obtained in all subsequent cases.

Apart from acute MR reduction, the most significant result in terms of efficacy observed in this study is the reduction of the septolateral mitral annular dimension observed after the final adjustment (*Figure 7*). The majority of surgeons prefer to perform undersized annuloplasty with a complete rigid ring to address MR.

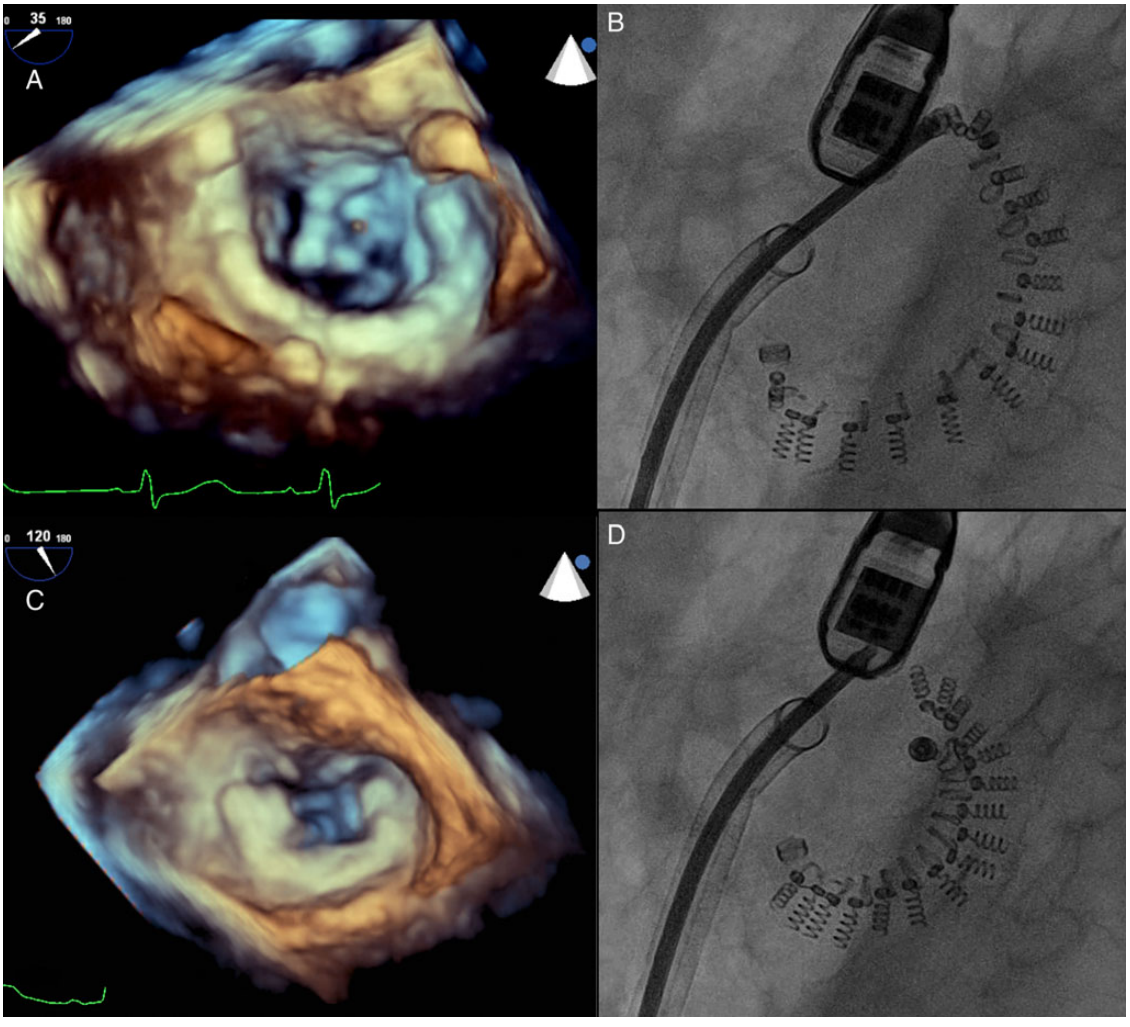


Figure 7 Three-dimensional echocardiography surgical view and fluoroscopic view of the Cardioband before (*A* and *B*, respectively) and after final adjustment (Panels *C* and *D*).

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For many years, both partial and complete rings have been used in patients with MR. The use of a complete ring has recently been associated with increased freedom from recurrent significant MR at follow-up.[22] However, surgical experience suggested that the main determinant for repair durability after undersized annuloplasty in MR is the achievement of good leaflet coaptation rather than the type of ring: a coaptation length of at least 8 mm should be obtained to ensure a durable repair.[9,10] Coaptation length is strictly related to the reduction in septolateral dimension. After the final adjustment, we were able to obtain a more than 21% reduction in septolateral dimension, which is comparable with that obtained after surgical undersized annuloplasty with a complete ring (22% with Edwards Physio II ring and 25% with the IMR ETlogix ring).[23] Compared with conventional surgical rings, the possibility of beating-heart adjustment of the Cardioband may allow optimizing the reduction in septolateral diameter and the final coaptation length.

Clinical role of transcatheter mitral valve annuloplasty

The introduction of a reliable annuloplasty device does not prevent the eligibility of other transcatheter interventions in the future. About 20% of the patients still have residual MR after MitraClip, and only a minority of patients undergoing MitraClip treatment has $<2+$ MR after the procedure.[21,24,25] Considering that surgical experience has shown that long-term results of edge-to-edge mitral valve repair in the absence of annuloplasty are suboptimal,[26,27] the absence of mitral valve annuloplasty is a concern regarding the durability of MitraClip treatment. Moreover, some patients screened for MitraClip have been denied therapy due to anatomical ineligibility due to annular dilatation, suggesting that there is a clinical need for an adjunctive transcatheter mitral repair approach.[28] Although the Cardioband device is currently primarily intended for use in the treatment of MR, the combination of devices may become an alternative for patients with diverse aetiologies and more complex anatomies.

Compared with MitraClip, the Cardioband is a pure anatomical implant. The device is implanted directly on the atrial side of the posterior mitral annulus using a standardized technique. This feature, together with the high safety profile and the preserved option for future transcatheter MV replacement, makes the Cardioband an ideal device for early indication in the field of catheter-based mitral treatment.

Conclusion

This study demonstrates the feasibility and safety of percutaneous direct mitral annuloplasty with the Cardioband device in high-risk patients with MR. Acute efficacy is comparable with that observed with transcatheter edge-to-edge mitral valve repair. Further investigation is needed to assess the durability and the long-term outcome.

This technology, based on a solid surgical background, is a promising tool to improve the results of transcatheter mitral valve interventions. It has the potential to expand the overall number of patients who could benefit from a transcatheter mitral intervention and to improve the efficacy and the durability of the currently available techniques, by the combination of annular and leaflet repair in selected patients.

Authors' contributions

F.M. and M.T. performed statistical analysis; F.M. handled funding and supervision; F.M., M.T., G.N., C.H., A.V., D.M.-Z., S.B., M.H., O.A., A.C., G.L.C., E.A., M.Z., F.T., Y.T., F.K., and K.-H.K. acquired the data; F.M.: Conceived and designed the research; F.M. and M.T.: Drafted the manuscript; F.M., M.T., G.N., C.H., A.V., D.M.-Z., S.B., M.H., O.A., A.C., G.L.C., E.A., M.Z., F.T., Y.T., F.K. and K.-H.K.: Made critical revision of the manuscript for key intellectual content.

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Conflict of interest: F.M., G.N., A.V., O.A., A.C., and K.-H.K. declare an economical relationship with Valtech.

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