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**Transcatheter mitral annuloplasty
for functional mitral regurgitation
with Edwards Cardioband Mitral
Reconstruction System**

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A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered current, but may change as more evidence becomes available if an update of the document is commissioned.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology/procedure: **Transcatheter mitral annuloplasty for functional mitral regurgitation with Edwards Cardioband Mitral Reconstruction System (Cardioband MI)**

Target population

Symptomatic patients with functional mitral regurgitation (FMR) in which complete and properly coaptation of leaflets fails because of mitral annular dilation secondary to left ventricle enlargement.

Description of the procedure and technology

The Cardioband MI is a catheter-based device that functions as a percutaneous annuloplasty band. Utilizing a transvenous and transeptal approach, the Cardioband MI is implanted on the posterior mitral annulus from the anterolateral to the posteromedial commissure, with intraprocedural adjustment to reduce the septolateral diameter of the mitral annulus and restore leaflet coaptation [Yucel, 2017]. The Cardioband MI system is a transcatheter direct annuloplasty delivered by transeptal approach and performed under general anaesthesia with 3D transesophageal echocardiography (TEE) guidance. The transeptal steerable sheath (TSS) is advanced over a super-stiff guide wire into the left atrium. The implant delivery system (IDS) is then advanced through the TSS [Maisano, 2016]. The delivery system is steered, until the tip of the implant catheter (IC) is placed over the anterior commissure and a sequence of multiple anchors is implanted from the antero-lateral to the postero-medial commissure. The whole procedure is done from the atrial site with no interaction with the left ventricle [Taramasso, 2014]. 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 MI 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 [Maisano, 2016]. The last anchor is then deployed and the implant disconnected from the IDS is subsequently removed. The size adjustment tool (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 [Maisano, 2016].

Adequate reduction of mitral regurgitation (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 [Maisano, 2016].

Clinical importance and burden of disease

MR occurs when the mitral valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. MR can be acute or chronic. The latter is a long-term disorder associated with valvular or ventricular pathologies.

In patients with chronic MR, the regurgitation causes left ventricular volume overload that, overtime, induces ventricular remodelling that causes excessive chamber dilatation not compensated by adequate hypertrophy, with decreased myocardial contractility and efficiency [Maisano, Alamanni, 2014]. An enlarged atrium may

develop atrial fibrillation which reduces the heart's ability to pump efficiently [AHA, 2018]. Progressive myocardial degeneration may finally lead to irreversible dysfunction and end-stage heart failure (HF) [Beerli, 2007]. According to the aetiology, MR can be degenerative (also named primary) or functional (secondary) [EUnetHTA JA2 Pilot SB-15]. Degenerative MR (DMR) covers all aetiologies in which intrinsic lesions affect one or several components of the mitral valve apparatus and is the most common in western countries counting 60–70% of MR in patients undergoing surgery [lung, 2003; Nkomo, 2006; Enriquez-Sarano, 2009]. Functional MR (FMR) is instead characterised by dysfunction of structurally normal mitral valve leaflets due to tethering by an abnormal left ventricle or annular dilation. This condition is observed in patients with abnormal left ventricular wall motion or dilated cardiomyopathies but can also exist in patients with normal mitral valve leaflet motion where MR persists and complete coaptation fails because of mitral annular dilation, often in presence of remodelling due to long standing atrial fibrillation [Renew, 2018]. Because FMR is associated with normal valve leaflets, it is commonly categorised as a disease of the ventricle [De Marchena, 2011].

Even if FMR is associated with worse outcomes, such as increased mortality and hospitalisations for heart failure, its optimal treatment regimen is much less clear if compared with DMR, and there is significant interest in identifying optimal treatment strategies [Renew, 2018]. Pharmacological approaches, based on beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists, as well as cardiac resynchronisation therapy (CRT), have been shown to improve outcomes and decrease MR severity. Surgical approaches to manage FMR are not supported by strong levels of evidence and recommendations on percutaneous interventions are made on the basis of poor evidence within the latest guidelines of the European Society of Cardiology (ESC) [Baumgartner, 2017].

The incidence of MR varies across regions. Estimates of severe MR in the Italian population range from 8,528 to 32,000 new patients per year [Bedogni, 2017]. However, epidemiological data on isolated FMR are very limited. A recent cohort study on 1,294 community residents in the US showed that 571 (44%) had DMR and 723 (56%) had FMR [Dziadzko, 2018]. Interestingly, only 5% of FMR patients underwent mitral surgery while DMR was managed with such approach in 29% of the cases. This may be related with to uncertainties regarding effectiveness of surgery for FMR described above.

Products, manufacturers, distributors and approval

Cardioband MI is a device manufactured by Valtech Cardio Ltd and from 2017 is branded as Edwards Lifescience. The device is classified according the *Classificazione Nazionale dei Dispositivi Medici (CND)* under the class “P07030499 – ANELLI VALVOLARI CARDIACI – ALTRI” and registered within the Italian National medical device database (BD/RDM) with the numbers 1354157, 1589133-37 related to the six different sizes (range) to cover the different annulus sizes (min. 73 mm; max. 120 mm).

Cardioband MI is a single-use Risk Class III medical device that received the CE mark in 2015 and is indicated for the reconstruction and/or remodeling of mitral valves subject to pathological changes. The device is not approved by the FDA.

Cardioband MI is an adjustable annuloplasty system that includes the implant and three main accessories:

1. The implant is a polyester sleeve with radiopaque markers. The sleeve is mounted on the delivery system and the anchor deployed from the internal part. A contraction wire enables shorten the implant. The implant size is adjusted to the patient's needs under TEE guidance and the size can be completely reversed [IFU; Maisano, 2016].
2. The Cardioband MI delivery system consists of the implant delivery system (IDS) and the trans-septal steerable sheath of 25F. The IDS comprises a steerable guide catheter and an implant catheter with the Cardioband MI implant mounted on its distal end [IFU; Maisano, 2016].
3. The anchor drivers that are used to fasten the Cardioband MI implant to the annulus and are made in stainless steel with 6 mm long anchors. The anchors are fully repositionable and retrievable until deployed [IFU: Maisano, 2016].
4. The size adjustment tool that has a distal tip connected over the implant wire and is used to control the implant adjustment spool and the implant size [IFU; Maisano, 2016].

Optional medical, are presented in Table 1.

Description	RDM/BD code	Risk Class
Cardioband delivery system	1354209	III
Cardioband anchor drives	1354223	III
Cardioband stand	1354702	I
Cardioband booster kit	1354684	I
Cardioband GC-IC fixator	1354716	I

Table 1: Cardioband MI accessories.

Product name [Manufacturer]	Distributor	CE Mark	BD/RDM	FDA
Edwards Cardioband Mitral Reconstruction System (Valtech Cardio now Edwards Lifesciences)	Edwards Lifesciences	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Setting

Cardioband MI is used in catheterisation lab (better in a hybrid operating room) during transcatheter mitral annuloplasty for FMR. The operating room must be equipped with an angiography system and ultrasound system with a TEE and TTE probes [IFU].

<input type="checkbox"/> Home	<input checked="" type="checkbox"/> Hospital	<input type="checkbox"/> Outpatient
<input type="checkbox"/> Accident and Emergency	<input type="checkbox"/> Other:	

Roll out in Italy

The manufacturer stated that, from Cardioband MI commercialization (2015) until today (July 2018), less than 1,000 procedures have been performed worldwide and 36 of them have been performed in Italy (12 of 36 implants were implanted in research setting, in patients enrolled in clinical study). Searches on the "Flusso Consumi - NSIS" (consulted on July 2018), a database held by the Italian Ministry of Health to register the acquisition of all medical devices in public hospitals, showed no units purchased in 2015, 5 units in 2016, and 6 units in 2017. According to the Italian Society of Cardiology (GISE) 14 implants were performed in 2016 and 16 in 2017 in public and private hospitals [GISE, 2018].

<input type="checkbox"/> Pre-marketing	<input type="checkbox"/> On the market for 1-6 months	<input type="checkbox"/> On the market for 7-12 months
<input checked="" type="checkbox"/> On the market for more than 12 months	<input type="checkbox"/> Not identified	

Comparators

Optimal medical therapy (OMT) (including CRT) or OMT plus conventional or minimally-invasive surgery with mini-thoracotomy approach.

Effectiveness and safety

The present report was carried out following the Agenas' Manual of Procedures [Agenas, 2014] and respecting the procedures outlined in the Agency's Plan for Transparency and Corruption Prevention (2017-2019) [Agenas, 2017].

The literature search was conducted in August 2018 on Pubmed, Embase, and the Cochrane Library, looking for studies reporting effectiveness and safety of the device Cardioband MI, published in Italian or English from 2013. We also searched the register www.clinicaltrials.gov.

The search strategy on electronic databases identified 178 records. After removing duplicates and assessing titles and abstracts, we evaluated 11 full-text articles for inclusion in our report. Seven relevant articles were included in the final analysis. Of the included studies, two were reviews [Ferrero, 2018; Saccocci, 2018], and five were observational studies [Arsalan, 2016; Maisano, 2016; Messika-Zeitoun, 2018; Nickenig, 2016; Pieri, 2017]. The studies by Maisano 2016 and Nickenig 2016 are included and described in Ferrero 2018.

The search on ClinicalTrials.gov identified seven studies; two of them were excluded because related to the device Cardioband tricuspid. The remaining five studies are described in Table 2. Only one of these five studies has a comparative design (ACTIVE trial, NCT03016975).

Description of included studies: reviews

The recent review by Ferrero et al. (2018) describes the main articles published on Cardioband MI, from the pre-clinical experience [Maisano, 2012], to the first-in-man implantation [Maisano, La Canna, 2014], the multicenter feasibility study [Maisano, 2016], and its results at 6-months [Nickenig, 2016] and at 1-year [Vahanian, 2017].

The feasibility non comparative and non-randomised study enrolled 31 high-risk patients with significant FMR in 7 European sites [Maisano, 2016]. All patients had $\geq 2+$ MR, and 24/31 patients had 3 to 4+ MR at baseline. The technical success rate, defined as complete implantation and reduction of septolateral dimension, was achieved in 29 of 31 patients. Adjustment of the Cardioband MI device resulted in a significant reduction (21.1%, $P < 0.001$) in the septolateral dimension in all study patients but two. After 1 month, 75% of the patients had 0 to 1+ MR, and 10.7% of the patients remained with 3 to 4+ MR. Thirty-day mortality was 6.5% (2/31). Other Serious Adverse Events (SAEs) were 2 MR recurrence (related to the device, i.e., partial anchor detachment at early phases), 2 renal insufficiency (possibly related to the procedure), 2 pericardial effusions (possibly related to the procedure), 1 open-heart surgery, 1 left femoral pseudo-aneurysm (related to the procedure), and 1 bleeding complication (related to the procedure).

Nickenig et al. (2016) reported six-month results, showing 13.6% of patients having 3 to 4+ MR, 31.8% with 2+ MR, and 54.5% of the cohort had 0 to 1+ MR ($p < 0.001$ compared to baseline). 18.2% of patients had New York Heart Association (NYHA) functional class III symptoms, 54% had NYHA functional class II symptoms, and 27% had NYHA functional class I symptoms ($p < 0.001$). The mean distance on the 6-min walking test (6 MWT) increased from 250 ± 107 m at baseline to 332 ± 118 m ($p < 0.005$) and quality of life assessed by Minnesota Living With Heart Failure Questionnaire improved over the 6-month follow-up from 38.2 ± 21 to 18.1 ± 10.9 ($p < 0.001$). Less than 20% of patients had MR recurrence at 6 months follow up. The authors concluded that in patients with impaired left ventricular (LV) function, FMR, and heart failure, mitral annuloplasty with the transcatheter Cardioband MI is feasible and safe. Annular dimension and FMR are significantly reduced and is associated with decreased heart failure symptoms and increased exercise capacity.

Vahanian et al. [Vahanian, 2017] reported 1-year follow up results for 39 patients (38 completed clinical follow up), showing 28% average reduction in septolateral diameter and maintained up one year, which carries functional improvement measured by 6 MWT and NYHA class demonstrating that the procedure effective and is also durable over time.

The review by Saccocci et al. [Saccocci, 2018], in addition to the studies already included in Ferrero et al.,

describes the results presented at the EuroPCR2017 congress [Maisano, EuroPCR 2017 congress] on a cohort of 61 patients showing 30-day outcomes: cardiac tamponade 1.6%, stroke 1.6%, need for elective mitral operation 1.6%, myocardial infarction 1.6%, major bleeding complication 3.3%, and a rate of 3.3% of mortality. The authors conclude that Cardioband MI safely reproduces a surgical procedure, with minimal invasion, preserving native anatomy, not precluding other different future interventions.

Description of included studies: observational studies

The study by Arsalan et al. [Arsalan, 2016] aims to assess the acute intraprocedural effects of transcatheter Cardioband MI device on 3-dimensional (3D) anatomy of the mitral annulus. Forty-five patients with FMR were enrolled in a single arm, multicenter, prospective study. Twenty-two of these patients having complete pre- and post-implant 3D (TEE) images were included. Cardioband MI was successfully implanted in all patients, and MR was reduced to moderate in 2 patients, mild in 17 patients, and trace of MR in 3 patients after final device cinching. Compared with preprocedural TEE, postprocedural TEE showed statistically significant reductions in annular circumference (137 ± 15 vs 128 ± 17 mm; $p = 0.042$), intercommissural distance (42.4 ± 4.3 vs 38.6 ± 4.4 mm; $p = 0.029$), anteroposterior distance (40.0 ± 5.4 vs 37.0 ± 5.7 mm; $p = 0.025$), and aortic-mitral angle ($117 \pm 8^\circ$ vs $112 \pm 8^\circ$; $p = 0.032$). Authors conclude that transcatheter direct mitral annuloplasty with the Cardioband MI device results in acute remodelling of the mitral annulus with successful reduction of FMR.

The paper by Messika-Zeitoun et al. [Messika-Zeitoun 2018] describes 1-year outcomes of sixty patients, enrolled between February 2013 and June 2016, with moderate or severe FMR on guideline-recommended medical therapy that were treated and analysed at 11 European institutions. The first patient was implanted in February 2013 and the last patient in June 2016. There were two in-hospital deaths (none judged device-related by authors): the first patient died of a haemorrhagic stroke a few days after device implantation while being treated by aspirin, ticagrelor, heparin and vitamin K antagonist; the second patient had a secondary dehiscence leading to severe MR recurrence and congestive heart failure and was operated on dying 4 weeks post-operatively. Furthermore there were one immediate post-procedural stroke, two coronary artery complications, and one tamponade. Anchor disengagement was observed in 10 patients (all but one were in the first 28 patients) and resulted in device inefficacy in five patients. Anchor disengagement resulted in only partial device detachment which may have impacted device efficacy but there was no device migration or embolization. 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 NYHA Class I/II), quality of life (-19 points on the Minnesota Living with Heart Failure Questionnaire score), and exercise capacity (+58 m by 6 MWT) improved significantly (all $P < 0.01$). The authors concluded that, 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 MI procedure did not preclude a secondary transcatheter mitral procedure.

The aim of the retrospective study by Pieri et al. [Pieri 2017] was to present the authors' preliminary experience with Cardioband MI device implantation. Thirteen patients underwent Cardioband MI implantation between February 2013 and April 2016. No complications related to anesthetic management were observed. Two intraoperative complications were recorded: 1 episode of device malfunction and 1 case of accidental damage to the circumflex artery. Postoperative complications were observed in 3 patients, involving detachment of the anchors, anemia requiring transfusions, vascular injury, and new-onset atrial fibrillation. Six patients were admitted to the intensive care unit (ICU) following the procedure; ICU stay was less than 1 day in 5 of these patients. At baseline, all the patients had severe MR; at hospital discharge, most of them showed improvement in MR degree compared with baseline: mild MR in 3/13, mild to moderate in 1/13, moderate in 3/13, moderate to severe in 4/13, remained severe in 1/13, and 1/13 patient was lost to follow up.

Description of included studies: trials on ClinicalTrials.gov

The ACTIVE Trial (NCT03016975) is an ongoing, prospective, multicenter, randomised, controlled trial. Patients with clinically significant FMR will be randomised 2:1 to receive either transcatheter mitral valve repair with the Edwards Cardioband System plus guideline directed medical therapy (GDMT) or GDMT alone. Patients will be seen for follow-up visits at discharge, 30 days, 6 months, and annually through 5 years. The estimated enrolment is of 375 participants. The study started on the 1st June 2017 and will finish on September 2024. The primary outcome measure is the prevalence of MR \leq 2+ and hierarchical comparison of device and control groups including time to cardiovascular death, number of heart failure hospitalizations, improvement in 6 MWT distance (in meters) and Kansas City Cardiomyopathy Questionnaire (KCCQ) (number of points improved) (Time Frame: 1 year).

MiBAND (NCT03600688) is an observational, prospective, single arm, European post-market study to assess the safety and efficacy of the Edwards Cardioband MI system. Patients will be followed up at 30 days, 1, 2 and 3 years. The estimated enrolment is of 200 participants; the study started on June 2018 and will finish on September 2022. The primary outcome is the number of participants with change in severity of MR at discharge relative to the baseline assessment (Time Frame: Hospital discharge; approximately 2-8 days post-procedure).

REPAIR (NCT02703311) is an interventional, single group assignment, open label study. Study objectives are to test the efficacy of the Cardioband MI in improving MR and heart failure symptoms in patients with symptomatic (NYHA Class III-IVa), severe MR in the post-marketing setting, and to evaluate the safety of the Cardioband MI system in the post-marketing setting. The estimated enrolment is of 50 participants; the study started on August 2016 and will finish on November 2019. The primary outcome measure is the reduction in severity of MR at 30 days of at least one category on a 0-4 scale (Time Frame: 30 days).

The main characteristics of these three studies, together with those of the other two studies in unknown status, are described in the Table 2.

Potential benefits to patients

The Cardioband MI system aims to reduce the annular septolateral dimension and MR severity, improving overall survival, survival free of readmission for heart failure, survival free of reintervention, functional status (NYHA class), exercise capacity (6 MWT) and quality of life for the treated patients.

<input checked="" type="checkbox"/> Mortality reduction or increased survival	<input checked="" type="checkbox"/> Reduction of the morbidity	<input checked="" type="checkbox"/> Improved quality of life (patient/users)
<input type="checkbox"/> Improved patient monitoring	<input type="checkbox"/> Other:	<input type="checkbox"/> Not identified

Cost of the technology/procedure

To analyse the economic aspects, related to technology object of this report, we carried out a research of the available evidence and, for the context data, we contacted the manufacturers through an *ad hoc* questionnaire sent by e-mail to collect information. Electronic searches to find economic evaluations and cost analysis on transcatheter mitral annuloplasty for FMR with Cardioband MI were performed on bibliographic databases (Pubmed, Embase and Cochrane Library) in August 2018. No economic studies and cost analysis were available from our research. This result was confirmed also by the manufacturer. According to the manufacturer, the list price of the Cardioband MI system is € 30,000.00 plus VAT (4%); the purchase price on market of the Cardioband MI system is € 23,000.00 plus VAT (4%). The procedure with Cardioband MI requires the disposables and supplies provided together with the Cardioband MI system. Disposables commonly used for transcatheter procedures, such as sterile gauzes, bags with heparinized saline, trans-septal kit, etc. do not have a relevant impact on the total cost of the procedure. Actually, the

Cardioband MI system is codified with DRG 104 (Intervention on cardiac valves and other major cardiothoracic interventions with cardiac catheterization) with a value of reimbursement equal to € 24,675.00 [Decreto del Ministero della Salute 18 ottobre 2012 - GU n. 23 del 28/01/2013].

<input checked="" type="checkbox"/> Increased costs compared to alternative treatments	<input type="checkbox"/> Increased costs due to increased demand	<input type="checkbox"/> Increased costs due to the required investments
<input type="checkbox"/> New costs	<input type="checkbox"/> Other: Reduction of costs linked to the reduction of re-intervention rate	<input type="checkbox"/> Not identified

Potential structural and organisational impact

Structural impact

There is no structural impact linked to the implant of Cardioband MI.

<input type="checkbox"/> Increase in requirement of instruments	<input type="checkbox"/> Always be used	<input type="checkbox"/> Can be used only under specific circumstances
<input type="checkbox"/> Decrease in requirement of instruments	<input checked="" type="checkbox"/> Other: no structural impact	<input type="checkbox"/> Not identified

Organisational impact

Annuloplasty procedures with Cardioband MI is performed by a trained physician (in endovascular and transseptal procedure and in the right use with Cardioband MI) and involve also different professional profiles such as a heart surgeon, a clinical cardiologist, an ultrasound physician and an anaesthetist. The heart surgeon presence also guarantees the management of any complications. According to the manufacturer, patients are selected jointly with Edwards Lifesciences specialists to ensure that the valve anatomy is compatible with Cardioband MI implant placement, evaluate the technical feasibility of the implant and establish the size of the most suitable Cardioband MI implant (using CT images). The manufacturer provides a preliminary theoretical and practical training of 1.5 day, and provides an additional support afterwards, to make the professionals autonomous in all phases of the procedure (patient selection and implant procedure) [Information provided by the manufacturer].

<input type="checkbox"/> Increase in the number of procedures	<input type="checkbox"/> Re-organisation required	<input checked="" type="checkbox"/> Training required for users
<input type="checkbox"/> Reduction in the number of procedures	<input type="checkbox"/> Other:	<input type="checkbox"/> Not identified

Conclusions

The device appears to be a possible alternative to current methods of MR repair. The available evidence shows high rates of technical success (>93%) allowing to obtain a significant reduction of the septolateral

diameter of the mitral annulus at 30-day, which persists in the assessments at 6 months and 12 months. Functional status (NYHA class), quality of life, and exercise capacity (6 MWT) improved significantly as well. However, given that no clinical trial evidence is available at present and current evidence base is restricted to a few observational studies, serious consideration should be given to the use of the device in a protocol-driven experimental setting only, after particular attention to patient selection to enrol in perspective studies (hopefully in comparative studies, with prior protocol registration).

Future prospects

Transcatheter direct annuloplasty is currently targeted by many companies and developers and it is extremely likely that many competitor devices will enter the market in the very near future. At the time of writing (August 2018), we were able to identify a plethora of systems under development and only one having the CE mark, the Mitralign Percutaneous Annuloplasty System (Mitralign Inc.; www.mitralign.com).

The Mitralign Percutaneous Annuloplasty System uses a surgical plication approach to treat FMR. The device is inserted through a trans-septal approach and uses a set of polyester pledgets that are anchored to the mitral valve leaflets, pulled together by a suture, and locked in place by a metallic lock to minimize the annulus. The Mitralign Percutaneous Annuloplasty System received the CE mark in February 2016 but it seems that the company decided to focus more on another product, the TriAlign System, based on the same technology platform but aimed to address tricuspid regurgitation. At the time of writing (August 2018) the Mitralign Percutaneous Annuloplasty System was not registered within the Italian RDM database and then could not be used in Italy. We run searches on clinicaltrials.gov database (21st September 2018) using the device name as a keyword to briefly report on the studies currently ongoing. No ongoing studies were identified on the Mitralign Percutaneous Annuloplasty System (while 2 ongoing studies were identified on the TriAlign System). Edwards Lifescience Corporation acquired certain assets of Mitralign, Inc., including intellectual property and associated clinical and regulatory experience.

Among the systems under development, mainly at a first-in-man stage, we can list Amend (ValCare Inc.; www.valcaremedical.com), AccuCinch (Ancora Heart Inc.; www.ancoraheart.com), IRIS (Millipede Inc.; www.millipedemedical.com), and TASRA System (MitraSpan Inc.; www.mitraspan-inc.com).

We run searches on clinicaltrials.gov database (25th July 2018) using the device name as a keyword to briefly report on the studies currently ongoing. Amend was under investigation within NCT02602613, a single group assignment study involving 40 patients and aimed to be completed within December 2018. AccuCinch was under investigation within three studies, NCT00800046, NCT03183895, and NCT02806570; they were all single group assignment studies involving 40, 132, and 35 patients respectively and aimed to be completed within September 2019, March 2013, and April 2014 respectively. IRIS was under investigation within NCT02607527, a single group assignment study involving 30 patients and aimed to be completed within December 2019. No studies were identified for the TASRA System.

Table 2: Summary of the registered studies on clinicalTrials.gov.

NCT number and Title	Condition	Purpose	Primary outcome	Study type and design	Intervention / Control	Estimated enrolment participants	Start and completion	Sponsor (s)
RECRUITING								
NCT03016975 Edwards Cardioband System ACTIVE Pivotal Clinical Trial (ACTIVE)	Functional Mitral Regurgitation; Mitral Regurgitation; Mitral Insufficiency	To establish the safety and effectiveness of the Edwards Cardioband System in patients with functional mitral regurgitation (FMR).	Prevalence of MR \leq 2+ and hierarchical comparison of device and control groups	Interventional Prospective, Multicenter, Randomized, Controlled Pivotal Trial	Intervention: Edwards Cardioband System plus guideline directed medical therapy (GDMT) Control: GDMT alone	375	Start date: June 1, 2017; Estimated completion date: September 2024.	Edwards Lifesciences
NCT03600688 Edwards Cardioband European Post-Market Study, MiBAND	Mitral Regurgitation; Mitral Insufficiency.	To assess the safety and efficacy of the Edwards Cardioband system. Patients will be followed up at 30D, 1, 2 and 3 years.	Number of participants with change in severity of Mitral Regurgitation at discharge relative to the baseline assessment	Observational Prospective, single arm, European post-market study	Intervention: Edwards Cardioband System	200	Start date: June 6, 2018; Estimated completion date: September 30, 2022	Edwards Lifesciences
ACTIVE, NOT RECRUITING								
NCT02703311 REPAIR - transcatheter REPAIR of mitral Insufficiency With caRdioband System	Mitral Regurgitation; Mitral Valve Insufficiency.	To test the efficacy of the Cardioband in improving MR and heart failure symptoms in patients with symptomatic, severe MR in the post-marketing setting, and to evaluate its safety in the post-marketing setting.	Reduction in severity of MR at 30 days of at least one category on a 0-4 scale	Interventional Single Group Assignment, Open Label	Intervention: Edwards Cardioband System	50	Start date: August 2016 Estimated completion date: November 2019	Edwards Lifesciences
UNKNOWN STATUS								
NCT01533883 Cardioband Adjustable Annuloplasty System for Minimally Invasive Mitral	Mitral Regurgitation; Mitral Insufficiency.	To evaluate the performance and safety of the Cardioband for repair of mitral regurgitation.	1) Overall rate of Serious adverse events (SAEs) and serious adverse device effects (SADE) until hospital discharge and at post-operative 30	Observational Cohort, Prospective	Intervention: Cardioband adjustable band	16	Start date: September 2011 Estimated completion date: June 2018	Edwards Lifesciences

NCT number and Title	Condition	Purpose	Primary outcome	Study type and design	Intervention / Control	Estimated enrolment participants	Start and completion	Sponsor (s)
Valve Repair			<p>days.</p> <p>2) Technical success rate of the implantation of the Cardioband</p> <p>3) Technical feasibility of Cardioband adjustment</p> <p>4) Reduce MR (at 30 days)</p>					
NCT01841554 Cardioband Adjustable Annuloplasty System For Transcatheter Repair of Mitral Valve Regurgitation	Mitral Regurgitation	To evaluate the performance and safety of the Cardioband Adjustable Annuloplasty System for repair of functional mitral regurgitation.	<p>Overall rate of Major Serious Adverse Events (SAEs)* and serious adverse device effects (SADE) until hospital discharge and at post-operative 30 days</p> <p>* Death, myocardial infarction, cardiac tamponade, device related cardiac surgery, stroke</p>	Interventional Single Group Assignment Open Label	Intervention: Edwards Cardioband System	51	Start date: April 2013 Actual Primary Completion Date: July 2016	Edwards Lifesciences

Evidence searches

Searches of the databases (Pubmed, Embase, and Cochrane Library) were carried out on August 2018 using the following keywords to indicate:

- **the technology/procedure:** cardioband, direct annuloplasty, direct ring annuloplasty, direct mitral annuloplasty, direct valve annuloplasty, direct ring mitral annuloplasty

Databases' searches were run using the following strategy consistently adapted to each of them:

#1 cardioband

#2 "direct annuloplasty"

#3 "direct ring annuloplasty"

#4 "direct mitral annuloplasty"

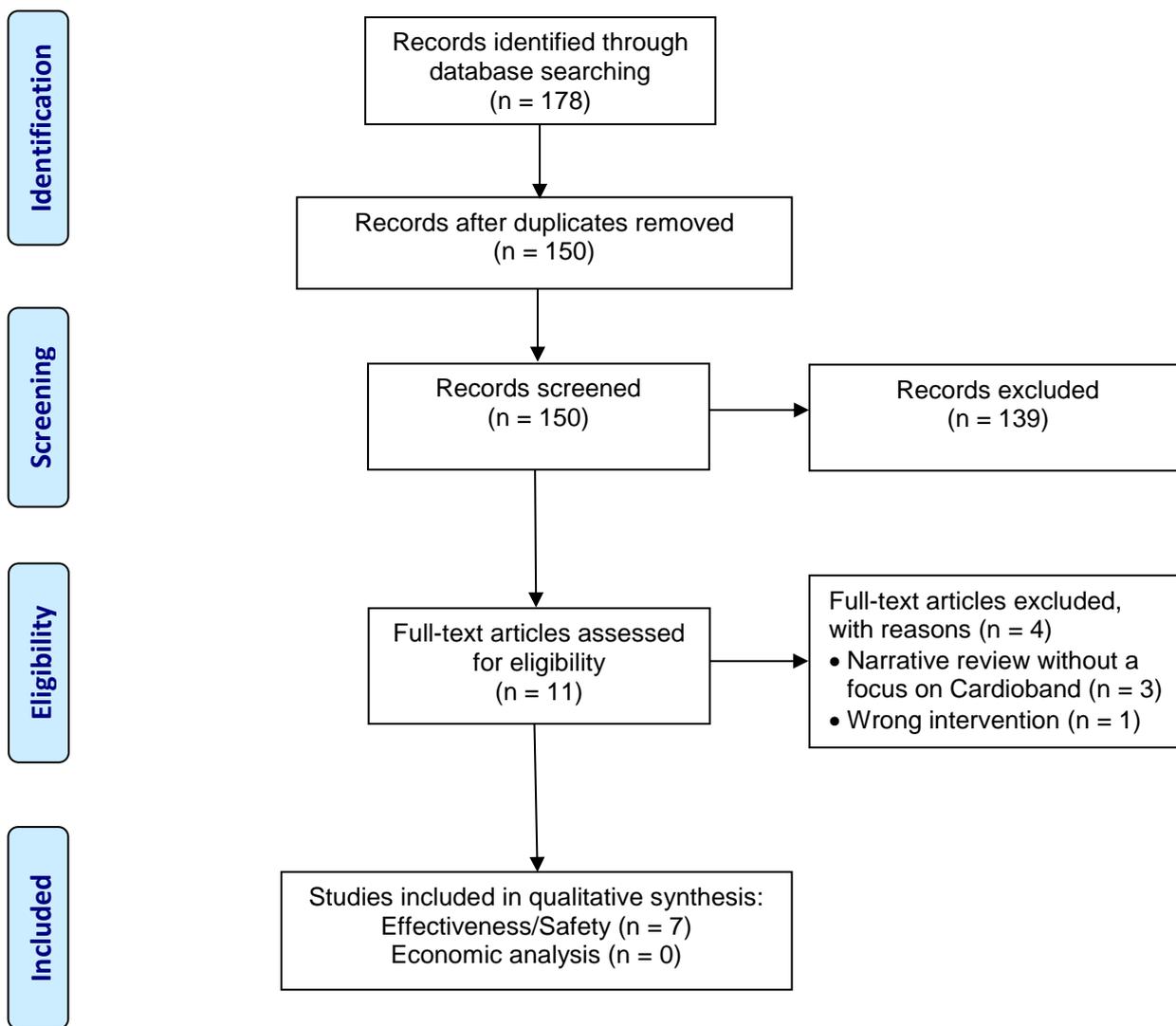
#5 "direct valve annuloplasty"

#6 "direct ring mitral annuloplasty"

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

The keyword "Cardioband" was searched on ClinicalTrials.gov.

PRISMA FLOW DIAGRAM



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Bibliography

Agenas http://www.agenas.it/images/agenas/hta/Manuale_procedure_HTA.pdf

AHA - American Heart Association http://www.heart.org/HEARTORG/Conditions/More/HeartValveProblemsandDisease/Problem-Mitral-Valve-Regurgitation_UCM_450612_Article.jsp#.WS2FpMZaZ-U (accessed, August 2018)

Arsalan, M., et al., Effect of Transcatheter Mitral Annuloplasty With the Cardioband Device on 3-Dimensional Geometry of the Mitral Annulus. *American Journal of Cardiology*, 2016. 118(5): p. 744-749.

Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Rev Esp Cardiol (Engl Ed)* 2018;71:110.

Bedogni F, Berti S, Esposito G, La Manna AG, Limbruno U, Marchese A, Mauro C, Salvi A, Santoro G, Tarantini G, Tarantino F, Varbella F, Violini R, Musumeci G. Transcatheter mitral valve repair for patients not amenable to surgical correction: epidemiology, diagnosis, equity of access, and economic impact. *G Ital Cardiol (Rome)*. 2017 Feb;18(2 Suppl 1):3S-8S.

Beeri R, Yosefy C, Guerrero JL et al. Early repair of moderate ischemic mitral regurgitation reverses left ventricular remodeling: a functional and molecular study. *Circulation* 2007;11;116(11 Suppl):I288-93.

Decreto del Ministero della Salute 18 ottobre 2012 - GU n. 23 del 28/01/2013.

De Marchena E, Badiye A, Robalino G et al. Respective prevalence of the different carpentier classes of mitral regurgitation: A stepping stone for future therapeutic research and development. *J Card Surg* 2011;26:385–92.

Dziadzko V, Clavel MA, Dziadzko M et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018 Mar 10;391(10124):960-969.

Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet* 2009; 373:1382–1394.

EUnetHTA JA2 Pilot SB-15. EUnetHTA Joint Action 2 Work Package 5 Strand B 5th Pilot SB-15 “Transcatheter implantable devices for MV repair in adults with chronic MV regurgitation”. Available from: https://www.eunetha.eu/wp-content/uploads/2018/01/Transcatheter-Implantable-Devices-for-mitral-valve-repair-in-adults-with-chronic-mitral-valve-regurgitation_Rapid-REA_Final_Sep-2015_0.pdf (accessed, August 2018)

Ferrero Guadagnoli, A., et al., Cardioband system as a treatment for functional mitral regurgitation. *Expert Review of Medical Devices*, 2018. 15(6): p. 415-421.

GISE, *Giornale Italiano di Cardiologia Invasiva*. Il Pensiero Scientifico Editore. Anno 2018 Volume15.

lung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;24:1231–1243. 2.

Maisano F, Vanermen H, Seeburger J, et al. Direct access transcatheter mitral annuloplasty with a sutureless and adjustable device: preclinical experience. *Eur. J. Cardiothorac. Surg.* 2012;42:524–529.

Maisano F, La Canna G, Latib A, et al. First-in-man transseptal implantation of a “surgical-like” mitral valve annuloplasty device for functional mitral regurgitation. *JACC Cardiovasc. Interv.* 2014;7:1326–1328.

Maisano F, Alamanni F, Alfieri O, et al. Transcatheter treatment of chronic mitral regurgitation with the MitraClip system: an Italian consensus statement. *J Cardiovasc Med (Hagerstown)* 2014;15(3):173-88.

Maisano F, Taramasso M, Nickenig G et al. Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial. *European Heart Journal* (2016) 37, 817–825

Maisano F. Clinical experience with Edwards Cardioband system for mitral regurgitation. *EuroPCR* 2017

Congress.

Messika-Zeitoun, D., et al., Transcatheter mitral valve repair for functional mitral regurgitation using the Cardioband system: 1 year outcomes. *European Heart Journal* (2018) 00, 1–7.

Nickenig, G., et al., Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation: 6-Month Results With the Cardioband Percutaneous Mitral Repair System. *JACC: Cardiovascular Interventions*, 2016. 9(19): p. 2039-2047.

Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005 –1011.

Pieri, M., et al., Anesthetic Management of Cardioband Implantation: Data From a Preliminary Experience and New Insights. *Journal of Cardiothoracic and Vascular Anesthesia*, 2017. 31(2): p. 482-488.

Renew JR, Martin AK, Murray AW, Pollak PM, Ramakrishna H. Functional Mitral Regurgitation: Interventions and Outcomes. *J Cardiothorac Vasc Anesth*. 2018 (4) [Epub ahead of print].

Saccocci M, Taramasso M, and Maisano F, Mitral Valve Interventions in Structural Heart Disease. *Current Cardiology Reports*, 2018. 20(6).

Taramasso M, Guidotti A, Cesarovic N et al., Transcatheter direct mitral annuloplasty with Cardioband: feasibility and efficacy trial in an acute preclinical model, *EuroIntervention*. 2016 Dec 10;12(11):e1428-e1434.

Vahanian, A. Multicentre trial results of the transcatheter mitral valve repair system for functional mitral regurgitation, presented at PCR London Valves 2017.

Yucel E, Santana O, Escolar E et al. Cardioband for the treatment of secondary mitral regurgitation: a viable percutaneous option? *J Thorac Dis* 2017;9(Suppl 7):S665-S667

Glossary

BD/RDM: Italian Medical device database

(<http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio>).

CND: Italian medical devices classification (Classificazione Nazionale dei Dispositivi Medici)

CRT: Cardiac resynchronisation therapy

DMR: Degenerative mitral regurgitation

FDA: Food and Drug Administration.

FMR: Functional mitral regurgitation

HF: Heart failure

IFU: instructions for use

MR: mitral regurgitation

TEE: Transesophageal echocardiography

TTE: Transthoracic echocardiography