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IM - REVIEW

One more option in heart failure: correction of mitral regurgitation with MitraClip®

Tommaso Bini[1] · Cecilia Agostini[1] · Miroslava Stolcova[1] · Francesco Meucci[1] · Carlo Di Mario[1]

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Abstract
Degenerative mitral regurgitation in elderly patients and functional mitral regurgitation secondary to severe left ventricular dysfunction are not easy options for conventional surgery. Recently, a new percutaneous approach has been proposed with the MitraClip®, based on the Alfieri edge-to-edge repair technique. The aim of the study is to report, compare and discuss the results of two multicenter randomized trials: MITRA.FR and COAPT in light of the current practice. In both trials patients with functional mitral regurgitation grade 3/4+ or 4/4+ were randomly assigned, in 1:1 ratio, to undergo percutaneous repair and optimal medical therapy or optimal medical therapy alone. Other baseline characteristics reflecting severity of mitral regurgitation and of left ventricular impairment were statistically different, such as the effective regurgitant orifice area (0.31 cm^2 in MITRA.FR vs 0.41 cm^2 in COAPT) and the indexed LVEDV (135 ± 37 ml/m^2 in MITRA.FR vs 101 ± 34 ml/m^2 in COAPT). A 24 months follow-up and a 12 months follow-up have been completed, respectively, in COAPT and MITRA.FR. Out of the 307 patients enrolled in the MITRA.FR, 152 were randomized to percutaneous treatment but only in 138 (95.8%) the MitraClip® was actually implanted. At the end of the follow-up a residual mitral regurgitation of at least grade 3+ has been observed in 17% of the patients. A composite of death from any cause or unplanned hospitalizations for heart failure at 12 months respectively occurred in 83 patients (54.6%) treated percutaneously and 78 patients (51.3%) treated with medical therapy only. A total of 614 patients have been enrolled in the COAPT and 293 underwent transcatheter treatment. A successful implantation of the MitraClip® was achieved in 287 patients (98.0%). Hospitalization for heart failure at 24 months occurred in 160 patients in the device group and in 283 in the control group, with an annualized ratio of 35.8% and 67.9%, respectively ($p > 0.001$).The conflicting results of the two trials may have many explanations, but probably the main cause is the most stringent inclusion criteria in COAPT. The effective reduction of mitral regurgitation and improvement in exercise capacity already observed in registries including more than 70,000 patients was confirmed in a randomized trial with improvement observed in hard end-points. This has already led to an extension of FDA approval to functional regurgitation and a more liberal use across the world.

Keywords Mitral valve · Mitral regurgitation · MitraClip

Introduction

Mitral regurgitation (MR) is the most common type of heart valve insufficiency in the United States. Acute and chronic MR affect approximately 5 in 10,000 people. Mitral-valve disease is the second most common valvular lesion, preceded only by aortic stenosis. In areas other than the Western world, rheumatic heart disease is the leading cause of MR. However, less than half of all physicians indicate high confidence in detecting clinically significant MR, underscoring the need for education on this topic [1].

Patients with MR fall into two general categories. One is primary mitral regurgitation; the other is secondary mitral regurgitation.

In primary MR, one or several components of the mitral-valve apparatus are directly affected. The most common cause of primary MR is degenerative disease, whether due to fibroelastic deficiency or myxomatous infiltration.

In contrast to primary MR, secondary (or functional) MR is associated with relatively normal mitral leaflet structure

✉ Tommaso Bini
tbini92@gmail.com

[1] Structural Interventional Cardiology, Department of Clinical and Experimental Medicine, University Hospital Careggi, Florence, Italy

and is typically attributed to myocardial pathological condition. MR results from an imbalance between closing and tethering forces on the valve secondary to alterations in LV geometry. It is most commonly seen in dilated or ischaemic cardiomyopathies. Annular dilation in patients with chronic atrial fibrillation and left atrium enlargement can also be an underlying mechanism [2].

Originally approved by the FDA only in patients with degenerative MR, the MitraClip® showed to have a similar feasibility and safeness even in case of functional MR [3–5].

Although not statistically significant, the duration of the procedure is longer and the number of the clips implanted is normally more in case of degenerative MR. This would suggest a more complex anatomical subset in this degenerative group which may be more technically demanding [5].

The right device for the wrong target

The progress in cardiac surgery led to a variety of techniques to repair myxomatous or fibroelastic degeneration and included leaflet resection, implantation of neochords or of a restrictive annulus. The simple technique of edge-to-edge repair invented by an ingenious Italian surgeon Ottavio Alfieri, had the distinct advantage to be easy to modify for a transcatheter approach. The MitraClip® (formerly e-Valve, now Abbott) consists in a 13 or 18 mm long nitinol clip wrapped in antithrombogenic PTFE designed to be delivered under fluoroscopic and transesophageal echocardiographic guidance [6]. A 24 Fr (8 mm) steerable sheath is introduced via a femoral vein and then advanced through a posterior and superior atrial transeptal puncture into the left atrium. Once the delivery catheter is advanced in the left atrium above the mitral leaflets generally at the site of maximal regurgitation, the arms of the clip and two grippers holding the leaflets from above are opened and rotated to be perpendicular to the commissural rim. The clip is then advanced into the ventricle and withdrawn till the mitral leaflets rest on the arms and can be grasped lowering the grippers and closing the arms, resulting in a double-orifice mitral-valve (Figs. 1, 2) [6, 7]. If the reduction of mitral regurgitation is insufficient the device can be reopened and its position adjusted or a second/third device can be implanted [6]. During the procedure UFH is administered to maintain ACT above 300 s, with patients, if not chronically anticoagulated, treated with aspirin for 6 months and clopidogrel for 30–90 days after the procedure [6]. New iterations of the device recently became available with greater rigidity of the delivery tip allowing better directionality during advancement (NT), wider opening of the grippers above the arms ensuring easier grasping (NTR model) and larger arms (XTR) more suitable for degenerative redundant leaflets or very dilated mitral annulli with a wide gap in co-optation.

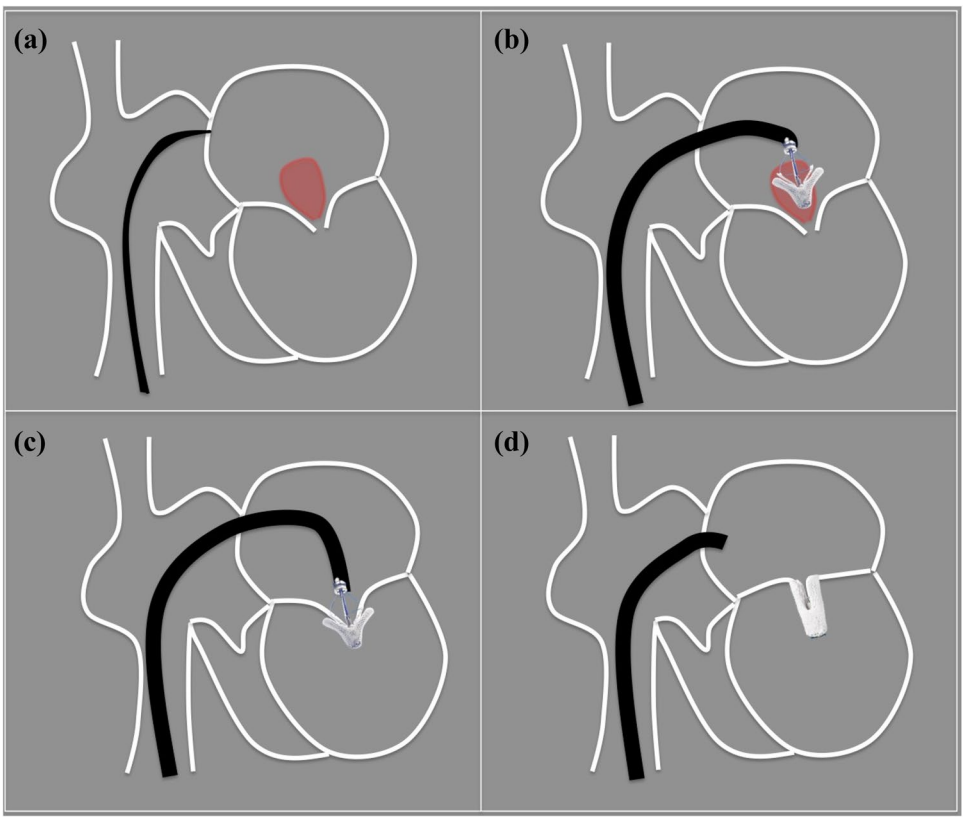


Fig. 1 MitraClip® implantation procedure. MitraClip® procedure requires a precise trans-septal puncture in a posterior and superior aspect of the fossa ovalis, at least 4 cm above the mitral annulus plane (**a**). The clip delivery system is then positioned above the regurgitant jet (**b**) and the clip is pushed through the mitral valve in a semi-open position with the grippers up (**c**). When a satisfactory contact is made between the clip and both the mitral leaflets, verified by transesophageal echocardiography, grippers are lowered onto the atrial aspect of the mitral leaflets and the clip is closed. Finally, if a good reduction of the regurgitant jet is achieved with the clip in a correct position, the clip delivery system is detached from the clip (**d**) and pulled back in the left atrium and eventually removed from the patient

Peri-procedural complications such as bleeding, stroke, and tamponade tend to occur [3–7].

The majority of MitraClip® procedures have been performed in general anesthesia. The motivation for this approach is mainly safety issues and the use of transesophageal echo [8]. Although general anesthesia may facilitate the management of peri-procedural complications and the use of TEE, this approach itself carries a potential risk for complications, such as hypotension episodes due to the vasodilatory effect of anesthetic drugs.

For these reasons a new approach with deep sedation has been proposed, resulting safe and feasible in most of the cases [8, 9].

After a MitraClip® procedure, rehabilitation is indicated (because of the underlying heart failure as well as the treatment of a heart valve). Here, optimization of drug therapy, implementation of standardized heart-failure training, the initiation of strength and endurance training and psychosocial support are initiated. Patients will be briefed on endocarditis prophylaxis lasting for at least 6 months. Furthermore, treatment with ACE inhibitors, beta-blockers and aldosterone antagonists is optimized. In particular, echocardiographic control in the rehabilitation clinic and by cardiologists has to be focused on a residual atrial septal defect, in transmitral gradient and a residual mitral regurgitation [3–10].

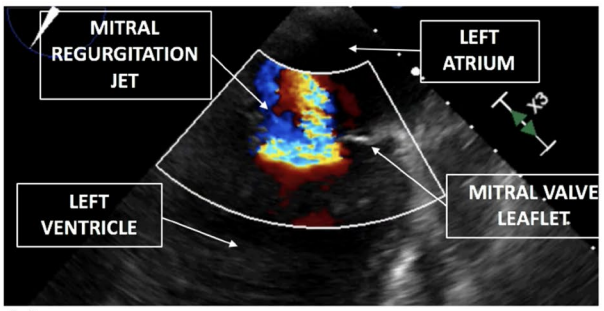
Caveats: the MitraClip® procedure has a steep learning curve and requires the implanter to be intimately familiar with all associated knobs and maneuvers before achieving optimal MR-reduction outcomes and minimizing procedure time. Also, certain anatomic features make MitraClip® procedure very difficult or not possible such as inter-atrial septal abnormalities, small atrial size (acute MR), leaflet tethering, large/small MV annulus, calcification or large flail gap or length. Moreover, surgical repair remains the gold-standard for primary organic MR in patients deemed operable due to improved short-term and long-term freedom from recurrent MR. Since residual MR is a predictor of recurrent progression of MR severity and adverse outcomes, MitraClip® usually limits any future repair attempts and is best reserved for patients at high risk for surgical repair.

As expected in the era of evidence-based medicine, the new device was immediately forced to go through the rigour of a randomized trial against the well-established surgical gold standard (Table 1). The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) multicenter trial enrolled 279 patients with severe degenerative mitral regurgitation suitable for MitraClip® implantation or surgery randomly assigned in a 2:1 ratio to percutaneous or surgical treatment. The primary composite end point for efficacy was freedom from death, surgery for mitral-valve dysfunction, and Grade 3+ or 4+ MR at 12 months. The primary safety end point was the rate of major adverse events at 30 days, defined as the composite of death, myocardial infarction, reoperation for failed mitral-valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 h, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood (Table 2) [6, 7]. The rates of death throughout the 5 years of follow-up were similar in the two groups (20.8% percutaneous-repair group vs 26.8% surgery group), while surgery or reoperation was more frequent in the percutaneous-treated patients (27.9% vs 8.9%). Despite the greater residual mitral regurgitation in the MitraClip® group, functional improvement was similar and results at 5 years showed a remarkable stability of the MR without further dilatation of the mitral annular area. As expected for a less-invasive approach, the lower efficacy was compensated by a greater safety with rates of major adverse events at 30 days of 15.0% in the percutaneous-repair group and 48.0% in the surgical group. These mixed results led to FDA approval of the device for degenerative MR but the ACC/AHA guidelines limited its use to patients who are at high surgical risk or inoperable [11].

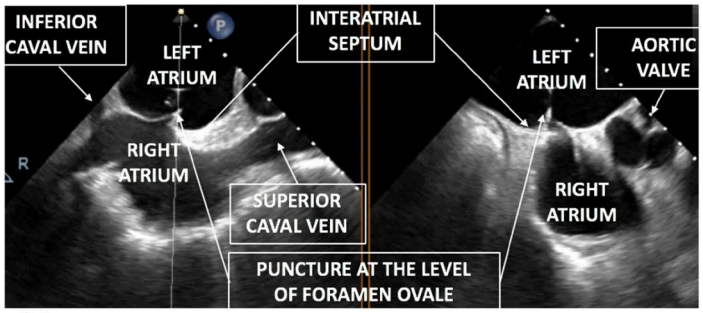
Functional MR due to ventricular remodeling is a growing burden because of heart failure due to ischemic or dilated cardiomyopathy. Severe MR (3+/4+) is a frequent consequence of left ventricular dilatation and has a considerable impact on the prognosis, in terms of mortality and hospitalization.

Despite the strict inclusion criteria some patients in the EVEREST trial and more in the Registry following the trial had functional or mixed rather than degenerative MR. The good results observed in this group also led to a gradual shift from degenerative to functional MR that became by far the most frequent indication in Europe, showing evidence of improved functional status and durable reduction of MR [12]. This practice was endorsed in part by the 2016 European Guidelines giving Class IIb indication to MitraClip® implantation for secondary MR in symptomatic heart-failure patients on optimal medical therapy and after cardiovascular resynchronization therapy, if indicated [13]. It seems a paradox for a device subject to the challenge of a randomized trial soon after its introduction, that more than 70,000 MitraClips® were implanted worldwide in the following 10 years mainly in HF patients before randomized trials were completed for its most frequent and logical indication.

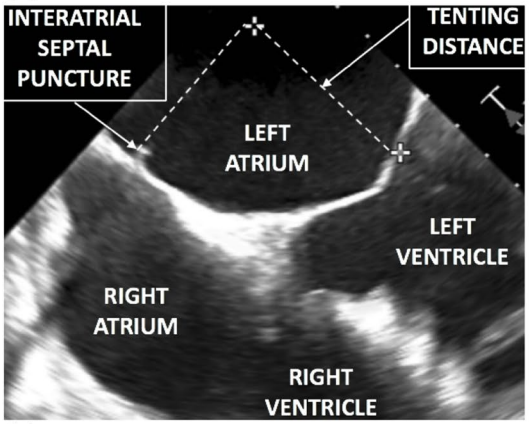
In the last decade more than 70,000 MitraClip® were implanted worldwide mainly in HF patients, a considerable number, especially if we assume that most of the randomized trial were still running to find the most frequent and logical indications for MitraClip®.


MITRAL REGURGITATION JET
LEFT ATRIUM
LEFT VENTRICLE
MITRAL VALVE LEAFLET

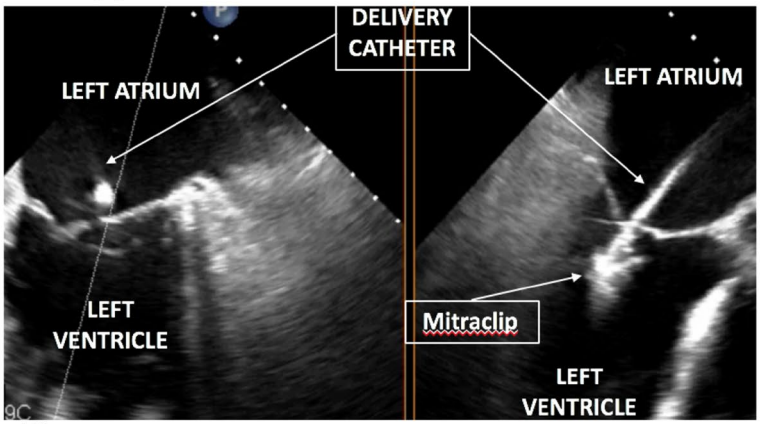
(a)


INFERIOR CAVAL VEIN
LEFT ATRIUM
INTERATRIAL SEPTUM
LEFT ATRIUM
AORTIC VALVE
RIGHT ATRIUM
SUPERIOR CAVAL VEIN
RIGHT ATRIUM
PUNCTURE AT THE LEVEL OF FORAMEN OVALE

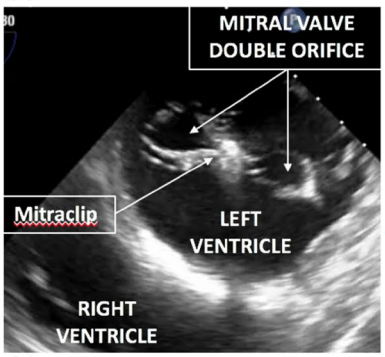
(b)


INTERATRIAL SEPTAL PUNCTURE
TENTING DISTANCE
LEFT ATRIUM
LEFT VENTRICLE
RIGHT ATRIUM
RIGHT VENTRICLE

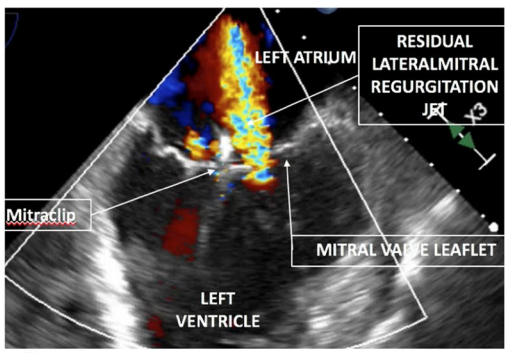
(c)


DELIVERY CATHETER
LEFT ATRIUM
LEFT ATRIUM
LEFT VENTRICLE
Mitraclip
LEFT VENTRICLE

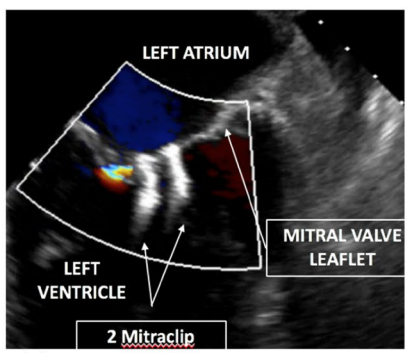
(d)


MITRAL VALVE DOUBLE ORIFICE
Mitraclip
LEFT VENTRICLE
RIGHT VENTRICLE

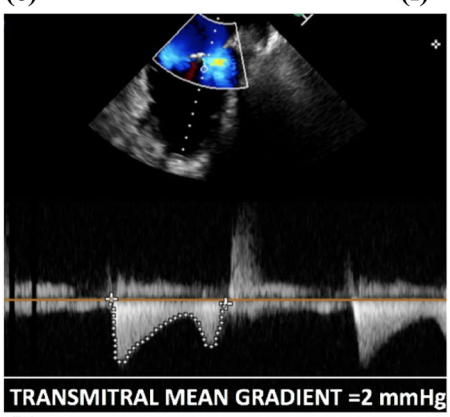
(e)


LEFT ATRIUM
RESIDUAL LATERALMITRAL REGURGITATION JET
Mitraclip
MITRAL VALVE LEAFLET
LEFT VENTRICLE

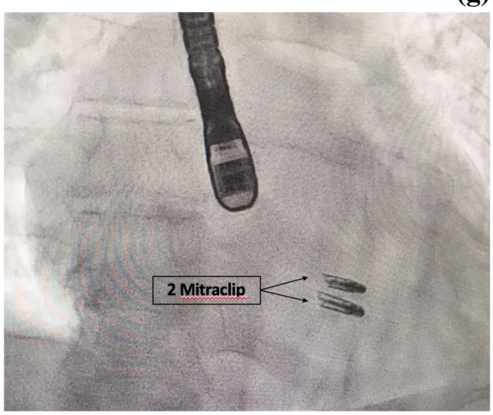
(f)


LEFT ATRIUM
MITRAL VALVE LEAFLET
LEFT VENTRICLE
2 Mitraclip

(g)


TRANSMITRAL MEAN GRADIENT =2 mmHg

(h)


2 Mitraclip

(i)

◂**Fig. 2** **a** Bicommissural view: severe regurgitant jet in a functional MR with a dysfunctional dilated ischemic LV. **b** Interatrial septum puncture at the level of foramen ovale. Xplane, left: bicaval view for superoinferior orientation, right: short axis view for the anteroposterior orientation. Thanks to Mullins' catheter the tenting area is appreciable. **c** To guarantee a proper maneuverability of the clip delivery system (in terms of movement, angulation and orientation of the catheter) it is required to measure the distance between the tenting area and the valve apparatus. **d** XTR MitraClip® is perpendicularly oriented to the mitral annulus, along the direction of the regurgitant jet, and then advanced in the LV through the catheter. When the device is correctly aligned, we proceed with the grasping of the leaflets. If a double orifice has been created and the echocardiography confirmed a significantly reduction in MR and a good grasping of the leaflets, the arms of the clip are closed, then blocked and at the end the clip is released. **e** Transgastric view: after the clip implantation on A2P2, we may observe a correct grasping of the leaflets with the creation of a double orifice. **f**, **g** After the placement of the first clip, there is still a residual lateral regurgitation. After placement of a second NTR clip more laterally there is minimal residual MR. **h** Mean residual transmitral gradient after the clips implantation = 2 mmHg. **i** Fluoroscopic view of the two clips at the end of the procedure. *LV* left ventricle, *LVOT* left ventricular outflow tract

New evidence in HF-MR

The MITRA.FR trial (Percutaneous Repair with the MitraClip® Device for Severe Functional/Secondary Mitral Regurgitation) is a multicenter, randomized, open-label trial, comparing percutaneous treatment with MitraClip® to optimal medical therapy in patients with heart failure and severe secondary MR. According to the European Consensus Document of Echocardiographic Standards, Grade 3+ or 4+ regurgitation was defined by echocardiography as a regurgitant volume of greater than 30 ml per beat or an effective regurgitant orifice area of greater than 20 mm^2. A total of 307 patients were enrolled and randomized to undergo percutaneous treatment or to receive medical therapy only. The study was conducted in France and coincided with the first introduction of this technology to the country. This explains why, out of 152 patients randomized to percutaneous treatment, MitraClip® was actually implanted only in 138 (90.7%) with 14.6% procedural complications, nearly double than in registries and in the US COAPT trial. Persistence of severe MR to greater or equal than 3+ was present in 9.1% post procedure rising to 17% at 12 months [14]. The primary efficacy end point, a composite of death from any cause or unplanned hospitalization for heart failure at 12 months, respectively, occurred in 83 patients (54.6%) treated with percutaneous repair and 78 patients (51.3%) with medical therapy alone [14].

Secondary end points were individual components of the primary outcome at 12 months and were also similar in the two groups, including unplanned hospitalization for heart failure, observed in 49% and 47% of patients treated with MitraClip® or medical therapy, respectfully.

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip® Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial [15] was a multicenter, randomized, controlled, parallel-group, sham-controlled trial, open-label to the implanters but with patients and physicians performing follow-up maintained blind throughout the duration of the study. A total of 614 patients treated in experienced centers of the United States and Canada were randomly assigned in a 1:1 ratio to the MitraClip® group or the control group. As in the previous study all patients had a secondary severe MR due to heart failure but the strictest guidelines of the US Echocardiography Society were used, resulting in a 10 ml greater regurgitant volume per beat. Unlike in MITRA.FR, extreme remodelling (LVESD greater than 70 mm) and systolic impairment (LVEF lower than 20%) were excluded. Besides a longer and more complete follow-up of 24 months has been obtained in the COAPT. A successful clip implantation rate of 98.0% and the immediate achievement of a MR grade of 2+ or lower in 94.8% of the patients in the device group were extraordinarily better than those observed in the EVEREST II but also substantially better than in the MITRA.FR trial, findings that probably reflect both increased operator experience and the introduction of high-resolution real-time three-dimensional transesophageal echocardiography [15, 16].

The primary efficacy end point, defined as all hospitalizations for heart failure at 24 months, occurred in 160 patients in the device group and in 283 in the control group, with an annualized ratio of 35.8% and 67.9%, respectively, a highly significant difference ($p < 0.001$). The 24-month risk of the composite of death from any cause was also significantly lower in the device group (29.1%) than in the control group (46.1%), $p < 0.001$. Additionally, quality of life (change in KCCQ score from baseline to 12 months 12.5 vs − 3.6; NYHA class I or II at 12 months 72.2% vs 49.6%), mitral regurgitation (MR ≤ 2+ at 12 months 94.8.0% vs 46.9%) and left ventricular remodeling (change in left ventricular end-diastolic volume from baseline to 12 months − 3.7 ml vs 17.1 ml) were all significantly better with device-based treatment [15].

The opposite results of MITRA.FR and COAPT trials may have several explanations with differences highlighted in Table 3. In the COAPT study pharmacological heart-failure treatment was implemented at maximal tolerated dose before randomization, with run-in phase when patients were excluded if their symptoms abated or if the degree of MR decreased [17]. This approach and the review of indications including the TEE images by an independent committee in the COAPT trial have ensured an optimal screening of patients with more refractory heart failure and persistent severe MR while in the MITRA.FR trial spontaneous improvement of MR and functional class occurred in almost 50% of patients in the patients with

Table 1 Anatomic inclusion criteria and relative/absolute contraindications

Optimal eligibility criteria	Unfavorable anatomical conditions
Pathology in A2-P2 zone	Commissural lesions
Mobile leaflet length ≥ 1 cm	Short posterior leaflet (avoid < 6–8 mm length)
Co-aptation length ≥ 2 mm	Severe asymmetric tethering
Co-aptation depth < 11 mm	Calcification in the grasping area
Flail gap ≥ 10 mm	Thickened mitral leaflets (rheumatic, post-irradiation)
Flail width ≥ 5 mm	Full thickness clefts
Mitral valve orifice area < 3.5–4 cm^2	Severe left ventricular remodelling
	Severe annular dilatation

Table 2 EVEREST trial

	EVEREST
Patients	279
Average EROA	0.56 cm^2
Primary endpoint for efficacy	100/184 (55%)
Residual MR > 2+ post-procedure	38/184 (21%)
Follow-up duration	12 months

EROA effective regurgitant jet, *primary endpoint for efficacy* freedom from death, from surgery for mitral-valve dysfunction and from 3+ or 4+ mitral regurgitation

Table 3 Differences MITRA.FR/COAPT

	MITRA.FR	COAPT
Patients	307	614
Average EROA	0.31 cm^2	0.41 cm^2
Average indexed LVEDV	135 ± 37 ml/m^2	101 ± 34 ml/m^2
Success rate	95.8% (138/144)	98.0% (287/293)
Complication	21/144 (14.6%)	25/293 (8.5%)
Residual MR > 2+ post-procedure	10/123 (8.1%)	11/210 (5.2%)
Follow-up duration	12 months	24 months

EROA effective regurgitant orifice area, *LVEDV* left ventricular end-diastolic volume, *success rate* correct clip implantation rate, *complication* device implantation failure, hemorrhage, atrial septum lesion, cardiogenic shock, cardiac embolism, tamponade, urgent conversion to heart surgery

only medical therapy [17]. A second possible explanation may be the differences in baseline valvular and ventricular characteristics between the patient populations of the two trials, with mitral regurgitation more severe and left ventricular end-diastolic volume smaller in the COAPT trial then in the MITRA.FR trial. Third, as discussed previously, examining complications and RMR improvement in the two trials, procedural performance may have differed between the two trials; a greater proportion of patients in the COAPT trial than in the MITRA.FR trial received more than one clip [17].

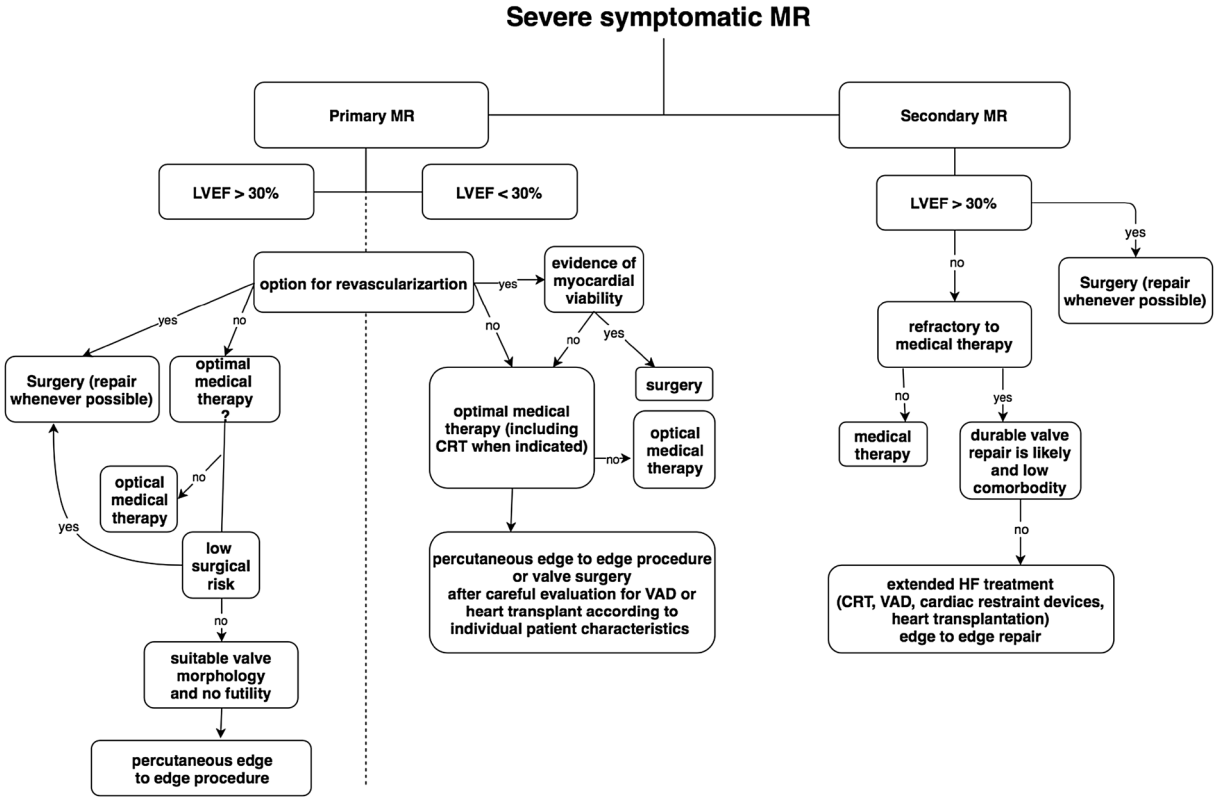
Nevertheless, the Kaplan–Meier curves of the two trials show a similar trend at 1 year, after which point the groups in the COAPT diverged [17]. As the MITRA.FR has a follow-up of 12 months, one may wonder what the results have been shown in case of a longer follow-up [17].

Practical consequences for heart team decision

Guidelines recommend that all patients considered for mitral interventions in general and MitraClip® in particular undergo a multi-disciplinary evaluation in a Heart Team, which should be composed of clinical cardiologists, structural interventional cardiologists, cardiac surgeons, specialists in cardiovascular imaging, cardiac anesthetists and other specialists in case of comorbidities (geriatricians for patients older than 75 years). Despite the theoretical equivalency of safety/efficacy endpoints in the surgical and device arms of the EVEREST trial, the better outcome of surgical repair makes it first-line treatment in patients without high risk for age or comorbidities. Fibroelastic degeneration in the elderly, often leading to rather acute clinical deteriorations because of chordal rupture, is a possible indication for MitraClip® if the anatomy is suitable and patients are considered at high risk (STS > 4–8%, age > 80–85 years, multiple comorbidities).

For functional MR, guidelines have not been updated after the presentation of the MITRA.FR and COAPT trials. The interpretation we follow in our hospital is that COAPT truly reflects the achievable improvements MitraClip® can offer when performed in the appropriate candidates with high operative standards by a dedicated interventional team while MITRA.FR reinforces the message that too advanced left ventricular impairment and small MR are not good indications for MitraClip® implantation. For functional MR the discussion should be between MitraClip® and medical therapy, while the surgical treatment should be considered only in case of concomitant coronary or aortic valve surgery (Table 4). Patients with admissions for heart failure or severely symptomatic should be systematically assessed for

Table 4 Management of severe symptomatic MR (modified from Baumgartner et al. [13])



LVEF left ventricular ejection fraction, *CRT* cardiac resynchronization therapy, *VAD* ventricular assist device

MR, paying attention to the dynamic nature of MR in heart failure. We should avoid overreacting to massive MR during acute decompensation but also avoid dismissing cases for MitraClip® when extreme intravenous diuretic and vasodilatory treatment have achieved a MR reduction that proves unsustainable over time. Occasionally, repeating echocardiography after exercise can be helpful to understand whether the increase in MR severity is the leading cause of low-threshold dyspnoea and impaired exercise capacity. These assessments should be performed after a sufficiently prolonged observation period under optimal medical therapy, including modern renin–angiotensin–aldosterone system inhibitors when tolerated and cardiac resynchronization therapy (CRT) if indicated. Futility should also be avoided, not only like for TAVI in terms of too-advanced cognitive impairment at old age or high expected mortality due to comorbidities but also of too-depressed LV function to allow an expected sufficient recovery. If suitable, these patients are better candidates for LV-assist devices or heart transplant.

With these caveats we believe that MitraClip® for functional MR is an important additional therapeutic option for heart failure which has now the evidence of an uncontroversial well-performed large trial confirmed by a very large real-life experience supporting device safety and quality of life improvement. Provided sufficient scrutiny has been given to the selection of candidates, the large reduction in mortality and recurrent hospitalization with number needed to treat (NNT) as low as 4 and 6 patients, respectively, offer sufficient benefit, far greater that after many universally used drugs or CRT. A specific health economics analysis has not been published but the impression is that the magnitude of the observed benefit amply covers the relatively high cost of the device (approx. 20,000 Euro per procedure, irrespective of number of clips implanted). For degenerative MR surgical mitral-valve repair remains the treatment of choice, with the MitraClip® offering an alternative only to elderly patients who are inoperable or at high risk for surgery.

Conclusions

The MitraClip® therapy is a safe and efficacious treatment option for both functional and degenerative mitral-valve disease. Originally approved only for patients with degenerative MR, the FDA has recently approved its use for functional MR too. Although surgery remains the treatment of choice, as suggested by the most recent guidelines, the MitraClip® is progressively gaining consensus between physicians for functional as well as degenerative MR, especially in elderly patients with comorbidities and high-surgical risk.

Authors' experience with MitraClip®

Since the introduction of this procedure 40 MitraClip® implantations have been performed by our team. Our team has never been involved in RCTs or registries regarding the MitraClip®.

Compliance with ethical standards

Conflict of interest Author B is member of a committee involved in the evaluation and the purchase of technical material for MitraClip® percutaneous implantation. The other authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Informed consent Informed consent was obtained from all patients for being included in the study.

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