Outcomes with percutaneous mitral repair *vs.* optimal medical treatment for functional mitral regurgitation: systematic review

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Abstract: Functional mitral regurgitation (MR) could be defined as a ventricular disease where mitral valve is structurally normal, left chambers are enlarged and mitral annulus is dilated with lack of coaptation of leaflets. Transcatheter mitral valve repair technique has broadened the therapeutic range in the treatment of severe MR. The aim of this study was to review outcomes of MitraClip *vs.* medical treatment for functional MR. We also planned to review the concept of functional MR, assessment of the degree, prognosis and therapy options. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Medline through PubMed database was used to search. The present review included manuscripts published between January 2009 and September 2019. Two authors independently screened titles and abstracts of all publications, and performed the selection of studies and data extraction. In the case of disagreements, consensus meetings reached the final decision. Inclusion criteria were: (I) randomized controlled trials and (II) works must compare MitraClip versus optimal medical treatment. Transcatheter mitral valve repair along optimal medical treatment has been compared with optimal medical therapy in two different randomized trials. In the COAPT trial, the MitraClip group showed a significant reduction in mortality and heart failure (HF) hospitalizations. In the MITRA-FR trial, no significant differences were observed between both groups. We reviewed important aspects of functional MR and performed a comprehensive review of both trials comparing them and focusing on their differences.

Keywords: Functional mitral regurgitation; heart failure (HF); MitraClip; transcatheter mitral valve repair

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Mitral regurgitation (MR) is an increasingly prevalent valve disease. Severe MR is associated with progressive dilation of the left ventricle (LV) and the onset of heart failure (HF). Patients with symptoms present an annual mortality rate >5% without any intervention (1,2). The treatment of MR varies depending on the patho-physiological mechanism.

In primary or degenerative MR one of the components of the mitral apparatus (leaflets, chords or papillary muscles) is affected and valve repair or replacement is recommended when there are symptoms, ventricular dilation, pulmonary hypertension or atrial fibrillation (3,4).

In secondary or functional MR, the components of

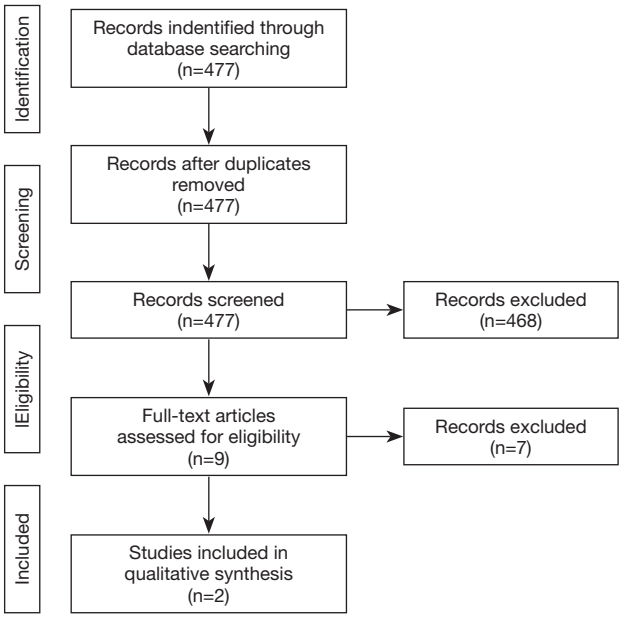

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) chart.

the mitral apparatus are intact; however, there is a lack of coaptation of the leaflets due to ventricular or annulus dilation. Patients with functional MR usually present LV dysfunction, and most of them undergo medical treatment. Mitral valve surgery could be considered when concomitant coronary artery bypass graft is required (3-5).

Transcatheter mitral valve repair technique has broadened the therapeutic range in the treatment of severe MR. The MitraClip system (Abbott; Menlo Park, California, USA) is a therapeutic option for patients with severe MR with high surgical risk (4,5). Treatment of patients with severe primary or degenerative MR with MitraClip has been shown to be safe and effective (6). Transcatheter mitral valve repair showed a reduction in the severity degree of MR and the improvement of functional class and quality of life (7,8).

While initial outcomes with MitraClip occurred in the field of primary or degenerative MR; most patients treated in registries had functional MR. In this group an improvement in functional class was observed in more than 75% of the cases (9-12), Therefore, transcatheter mitral valve repair along optimal medical treatment has been compared with only optimal medical therapy in two different randomized trials. In the COAPT trial (13), the MitraClip group showed a significant decrease in mortality and HF hospitalizations. In the MITRA-FR trial (14), no significant differences were observed between both groups.

The aim of this paper is (I) to review the concept, diagnosis and treatment options of the functional MR and (II) to know the clinical outcomes of the MitraClip versus medical treatment to treat functional MR.

Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15) (*Figure 1*). The Medline through PubMed database was used to search. The present review included manuscripts published between January 2009 and September 2019. It was performed using the following search series: ("Transcatheter mitral valve repair" OR "MitraClip" OR "Percutaneous mitral repair" OR "Transcatheter mitral repair") AND ("mitral regurgitation medical treatment" OR "functional mitral regurgitation medical treatment" OR "functional mitral regurgitation optimal medical therapy").

Study selection

Two authors independently screened titles and abstracts of all publications (477 manuscripts), and performed the selection of studies and data extraction. In the case of disagreements, consensus meetings reached the final decision. Inclusion criteria were (I) randomized controlled trials and (II) works must compare percutaneous treatment versus optimal medical management. The exclusion criteria of the study included language other than English, duplicates, letters to editor and case reports (*Figure 1*).

We also reviewed the concept of functional MR, assessment of the degree, prognosis, therapy options, and finally, the most important clinical evidence of the MitraClip in functional MR.

Functional MR

Definition, mechanisms and prevalence

Functional MR could be defined as a ventricular disease where mitral valve is structurally normal, left chambers are enlarged and mitral annulus is dilated with lack of coaptation of the leaflets. The LV dysfunction and dilation lead to the displacement of the papillary muscles towards posterior and apical, modifying ventricular geometry and causing failure of coaptation of the leaflets (16). Other uncommon mechanisms of functional MR are LV

dyssynchrony (17), and left atrial enlargement with annulus dilation due to atrial fibrillation (18).

Functional MR can be classified regarding the aetiology in ischaemic or non-ischaemic. The ischaemic aetiology is the most common. Non-ischaemic functional MR may be caused by different diseases: long-duration hypertension; idiopathic dilated cardiomyopathy; and myocarditis (16). Functional MR increases the preload, the stress of the LV wall and the LV workload, what contributes to a progressive HF situation within a vicious circle. Notably, the functional MR presents a dynamic nature (19).

The prevalence of moderate-to-severe functional MR varies from 6–29% in patients with diagnosis of chronic HF, increasing up to 75% in hospitalized patients due to acute HF (20).

Assessment of the severity degree of functional MR

The gold standard approach for the diagnosis of functional MR is the echocardiography. There are several echocardiographic parameters which are recommended to assess the severity degree of functional MR (4,5).

The European Society of Cardiology (ESC) guidelines define the functional MR as severe with an effective regurgitant orifice area (EROA) ≥20 mm^2, and a regurgitant volume ≥30 mL (4). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines define the functional MR as severe with an EROA ≥40 mm^2, and a regurgitant volume ≥60 mL (5).

These differences between ESC and ACC/AHA guidelines show that the evaluation of functional MR is challenging. However, functional MR is a dynamic condition and its severity degree may change depending on the loading conditions and the phase of cardiac cycle. Thus, it is recommended to assess the severity degree of the functional MR after the optimization of medical treatment (3).

Prognostic of functional MR

Several studies have shown that functional MR present a strong negative impact on the prognosis of patients with HF in relation to the severity degree (20-23). In a meta-analysis carried out by Sannino (22), which included 53 studies and 45,900 patients with and without functional MR; functional MR was associated with an increased risk of hospitalization due to HF (RR: 2.26; 95% CI: 1.92–2.67; P<0.001); cardiac mortality (RR: 2.62; 95% CI: 1.87–3.69; P<0.001); and all-cause mortality (RR: 1.97; 95% CI: 1.71–2.27; P<0.001) (22).

Therapy options

Optimal medical treatment and cardiac resynchronization

The medical therapy for patients with functional MR is the same that the guideline-directed treatment for patients with chronic HF. The optimal medical therapy which is recommended for patients with reduced LV ejection fraction and NYHA class ≥ II includes: beta-blockers; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; or angiotensin receptor–neprilysin inhibitor; mineralocorticoid receptor antagonists; and diuretics (24). The optimal medical treatment may promote LV reverse remodelling and improve the degree of functional MR (24).

Several studies have reported the role of cardiac resynchronization in reducing functional MR in patients with left ventricular dysfunction, wide QRS and HF symptoms at mid-term of follow-up (25,26). Thus, cardiac resynchronization is recommended by current guidelines in patients with LV dysfunction (≤35%); HF symptoms (NYHA class II–IV) despite optimal medical treatment; and a wide QRS complex on the electrocardiogram.

Cardiac resynchronization has shown to improve LV geometry and the degree of functional MR (27,28). Notably, three independent predictors of functional MR reduction after cardiac resynchronization could be highlighted: (I) an end-systolic dimension index <29 mm/m^2; (II) the absence of scar at the papillary muscle insertion; and (III) anteroseptal to posterior wall radial strain dyssynchrony >200 ms (29).

Surgical treatment

Despite the increased risk, patients with severe functional MR, that undergo coronary artery bypass graft, seem to benefit from mitral valve surgery (4,5). A randomized trial, which included 301 patients, showed that patients with functional MR, who underwent coronary revascularization surgery and mitral valve repair, presented an increased complication rate. There were no differences in LV reverse remodelling and mortality rate at 2 years follow-up (30). The role of mitral valve surgery for the treatment of isolated severe functional MR remains unclear. In this context, ESC guidelines suggest mitral valve surgery in patients with relevant HF symptoms despite optimal medical therapy, LV ejection fraction over 30%, and low co-morbidities (4).

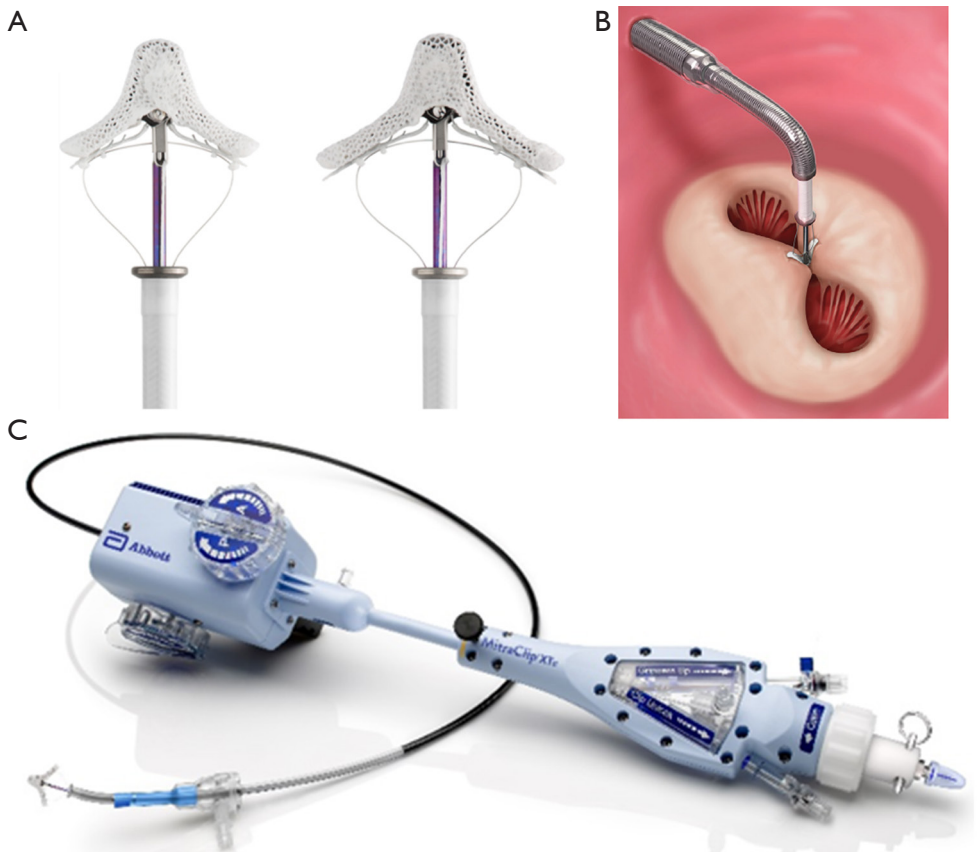

Figure 2 MitraClip™ (Abbott Vascular, Santa Clara, CA, USA). (A) MitraClip NTR on the left, and MitraClip XTR on the right; (B) MitraClip grasping mitral valve leaflets; (C) the clip delivery system. (Adapted with permission from Abbot. Images courtesy of Abbott. © 2019 Abbott. All Rights Reserved).

Transcatheter mitral valve intervention

Transcatheter edge-to-edge mitral valve repair

MitraClip system

The MitraClip (Abbott Vascular, Santa Clara, CA, USA) is a percutaneous device, which reduces the severity degree of MR by transcatheter approximation of the anterior and posterior mitral valve leaflets leading to a double-orifice valve similar to the Alfieri technique (6,7).

The MitraClip system consists of a steerable guide catheter and a MitraClip attached to the clip delivery system (*Figure 2*). The 24-Fr steerable guide catheter allows the introduction of the MitraClip delivery system, which is advanced through the guide into the left atrium via transeptal. A stabilizer keeps the system in the right position. The MitraClip consists of a cobalt-chromium clip with 2 arms covered by polyester (*Figure 2*). The tip of the guide catheter has a radiopaque marker. The steerable properties of the guide catheter and the MitraClip delivery system allow the precise orientation and positioning of the device. The delivery system is advanced to the point of maximum regurgitation guided by echocardiographic and fluoroscopic control (6,7). The arms can be opened and closed by a control mechanism on the MitraClip delivery system handle. On the inner of the arms are 2 grippers that help secure the leaflets. The use of the 3-dimensional transesophageal echocardiography in real-time is essential to guide the procedure, allowing to attempt the treatment of morphologically complex valves. Each leaflet is grasped between an arm and a gripper. When both leaflets are into the arms of the system, confirmed by transesophageal echocardiography, the MitraClip can be locked in the final position and released it if the result is adequate. Otherwise, the system can be re-opened and repositioned for a new attempt. The implant is performed in the cath

lab with general anesthesia (6,31) (*Figure 3*).

Last version of MitraClip is the XTR system (*Figure 2*). Compared with the first generation and the NT system, the MitraClip XTR has longer arms and grippers, which are designed to facilitate leaflet grasping in mitral valves with large coaptation gaps. In addition, the clip delivery system has been improved regarding navigation and clip positioning.

Transcatheter edge-to-edge mitral valve repair with MitraClip system has shown to be safe and effective for high-risk surgical patients with severe and symptomatic degenerative MR (32). There is scarce data regarding its use in functional MR. The ESC guidelines propose the use of the MitraClip only for symptomatic patients with severe functional MR despite optimal medical treatment (including cardiac resynchronization) and high surgical risk (4). The ACC/AHA guidelines do not report any indication for the MitraClip in patients with functional MR (5). The MitraClip system is contraindicated in patients who cannot undergo procedural anticoagulation or post procedural antiplatelet regimen; rheumatic mitral valve disease; active endocarditis; or evidence of thrombus.

PASCAL system

The PASCAL system (Edwards Lifesciences, Irvine, CA, USA) is a transcatheter mitral valve edge-to-edge repair device based on the tissue approximation with an anatomic spacer. This device consists of two wide and curved arms; two clips with capability of independent leaflet capture; and a nitinol woven spacer to optimize leaflet capture that leads to decrease the stress on the native mitral valve leaflets (33).

The CLASP Study (33), included 62 patients with MR that underwent transcatheter mitral valve repair with the PASCAL system. The successful implantation of the PASCAL device was achieved in 95% of patients. Major adverse events rate was 6.5% and all-cause mortality rate was 1.6% at 30 days follow-up. The PASCAL device showed to be feasible in decreasing the severity degree of MR; improving functional class, exercise capacity, and quality of life at 30 days.

Transcatheter direct annuloplasty mitral valve repair

Cardioband system

The Cardioband system (Edwards Lifesciences, Irvine, CA, USA) is a percutaneous mitral valve repair system, which most resembles a surgical annuloplasty ring. By interatrial approach, this device is implanted directly at the atrial side of the mitral annulus. First anchor is released in the lateral mitral commissure and additional anchors are released at short intervals until last one, which is implanted in the medial mitral commissure. Finally, the device is contract in order to remodel the mitral annulus with the aim of decreasing MR (34,35).

Messika-Zeitoun *et al.* (36), conducted a study including 60 patients undergoing Cardioband procedure, reporting a procedural success of 68% and a survival free of readmission for HF of 66% at 1-year follow-up.

Transcatheter indirect annuloplasty mitral valve repair

Carillon device

The Carillon Mitral Contour System (Cardiac Dimensions) consists of a distal and proximal anchor with a fixed length nitinol system that is released into the coronary sinus by a delivery system through the right external jugular vein. The distal anchor is released deep in the coronary sinus encircling the mitral annulus, and then traction is applied to constrict the coronary sinus and modify the annulus and reduce the MR (37).

The AMADEUS and TITAN trials showed safety and feasibility of Carillon device (38-40). The outcomes of the REDUCE-FMR trial at 12-month follow-up, have been presented at TCT congress 2019. The REDUCE-FMR trial randomized 120 patients, with dilated cardiomyopathy and moderate-to-severe functional MR, to Carillon implantation (87 patients) *vs.* sham control (33 patients). The primary efficacy endpoint of decrease in regurgitant volume was –7.1 *vs.* 3.3 mL (P=0.03) at 1 year follow-up. The mean change in LV end-diastolic volume was –10.4 *vs.* 6.5 mL (P<0.05). No differences in HF hospitalizations were found at 1-year follow-up.

ARTO system

The ARTO system (MVRx Inc., Belmont, CA, USA) consists of an interatrial septal anchor connected to a coronary sinus T-bar by a polyethylene suture, which is tensioned to decrease the anteroposterior diameter of the mitral annulus. The MAVERIC trial (phase I) (41), which included 11 patients undergoing ARTO implantation, showed safety of the device, with reduction of MR, LV size, and improvement in NYHA functional class at 30-day follow-up. Two-year follow-up showed stable safety and efficacy compared to 30-day findings.

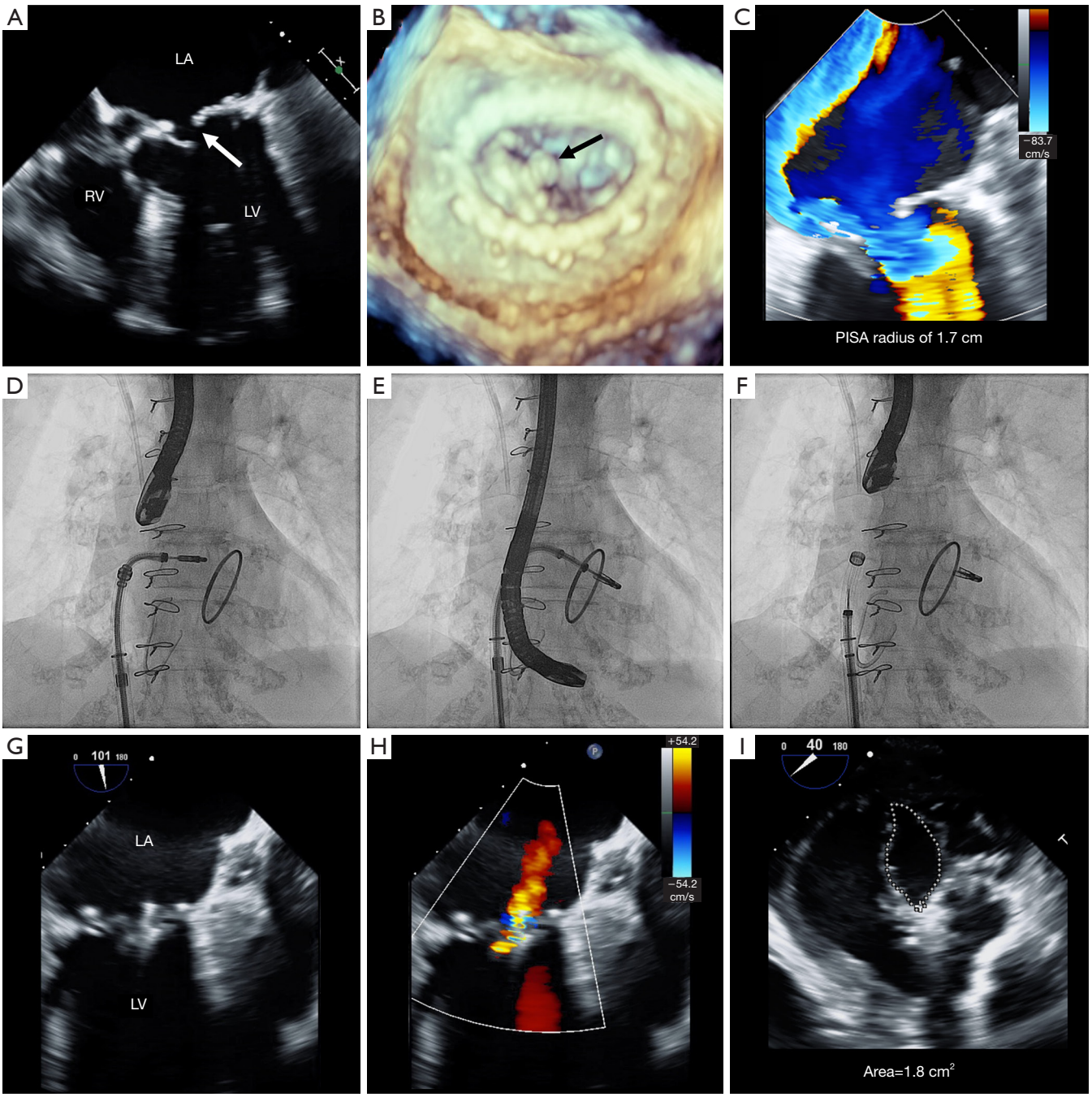

Figure 3 Clinical case of MitraClip after failure of previous surgical repair with annuloplasty. (A) Severe mitral regurgitation; a mid (P2 towards P1) portion of the posterior mitral leaflet is flail due to ruptured chordae, with a flail gap that measures 6 mm (white arrow); (B) three-dimensional transesophageal echocardiography showed flail posterior leaflet (black arrow); (C) severe mitral regurgitation with a PISA radius of 1.7 cm; (D,E,F) transcatheter mitral valve repair (fluoroscopy); (G,H) after the MitraClip implantation, mitral regurgitation reduced to mild; (I) mitral valve area post-MitraClip of 1.8 cm².

Clinical evidence on MitraClip

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II was the first trial of the MitraClip therapy, including 279 patients randomized to MitraClip therapy or surgical treatment (6). The MitraClip procedure showed to be safer and reported similar improvements in clinical outcomes (6). Notably, patients included in EVEREST II were low-risk surgical patients mainly affected by degenerative MR (73.4%) (6).

There are available data from several multicenter registries, mostly including patients with functional MR (7,10,12,42,43). MitraClip observational studies showed that transcatheter mitral valve repair is a safe procedure with low complication rates; effectively in reducing MR; and improves symptomatology and the quality of life (7,10,42,43). The outcomes of these registries suggest that MitraClip may improve prognosis. However, LV geometry and dysfunction, high levels of natriuretic peptides, and the impairment on NYHA class may suggest a worse prognosis in patients undergoing MitraClip.

MITRA-FR and COAPT trials

Only these two trials met the inclusion criteria of our systematic review. These trials were carried out to investigate the role of the transcatheter mitral valve repair in patients with functional MR and HF symptoms (class II-IV NYHA) despite optimal medical treatment (*Figure 1*) (13,14).

The MITRA-FR trial (Percutaneous Repair with the Mitra-Clip Device for Severe Functional/Secondary Mitral Regurgitation) (14), included 304 patients, all of them with chronic HF, left ventricular dysfunction, and severe functional MR, that were randomized to MitraClip therapy or only medical treatment. The MITRA-FR trial was major conducted by researchers in France (*Table 1*). Both groups show similar risk of hospitalization due to HF and risk of death at 12 months of follow-up. All all-cause mortality showed a hazard ratio of 1.11 (95% CI: 0.69–1.77); and hospitalization due to HF showed a hazard ratio of 1.13 (95% CI: 0.81–1.56). Despite the MitraClip group did not decrease LV volumes at 1-year follow-up; this group of patients showed a decrease in the degree of regurgitant volume at short-term (14).

The COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) (13), included 614 patients with chronic HF, left ventricular dysfunction, and moderate-to-severe or severe functional MR, that were randomized to transcatheter mitral valve repair or only medical treatment. The COAPT trial was carried out principally in the US and Canada (*Table 1*). The MitraClip group showed a lower risk of hospitalization due to HF, and a lower risk of death for any cause at 2 years of follow-up. The annualized rate of hospitalizations for HF showed a hazard ratio of 0.53 (95% CI: 0.40–0.70; P<0.001) at 2 years. All-cause mortality showed a hazard ratio of 0.62 (95% CI: 0.46–0.82; P<0.001) at 2 years. The MitraClip group showed a significant decreased of LV volumes at 1-year follow-up, in contrast with the outcomes of the MITRA-FR trial (13).

The outcomes at 3-year follow-up of the COAPT trial were presented at TCT congress 2019. The MitraClip showed to be safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality of life and functional capacity compared to optimal medical treatment alone. In addition, patients assigned to only optimal medical treatment who crossed-over and received a MitraClip experienced fewer HF hospitalizations and deaths or HF hospitalizations within 12 months than those who did not crossover, with rates comparable to patients originally assigned to the MitraClip.

Differences between the MITRA-FR and COAPT trials

Inclusion criteria and baseline characteristics (Tables 1,2)

The EROA and regurgitant volume were different between both trials, lower in MITRA-FR (EROA >20 mm²) compared to COAPT (EROA >30 mm²) (13,14). In the MITRA-FR, it was required at least one hospitalization due to HF in the previous 12 months for randomization. Nevertheless, the COAPT trial did not require a recent hospitalization (13,14). However, in the COAPT trial (13), a patient could be included if BNP ≥300 pg/mL or NT-proBNT ≥1,500 pg/mL. The MITRA-FR had no restrictions on LV dimensions (14). The COAPT required a LV function between 20–50% with LV end-systolic diameter <70 mm (13). In the COAPT trial, moderate-to-severe right ventricular dysfunction and/or severe pulmonary hypertension were exclusion criteria (in contrast to MITRA-FR).

Thus, the patients included in the MITRA-FR compare to the COAPT had less severity of functional MR (EROA:

Table 1 The MITRA-FR and the COAPT trials

Features	MITRA-FR trial	COAPT trial
Design		
Study type	Prospective, randomized (1:1)	Prospective, randomized (1:1)
Setting	France	United States and Canada
Centers	37	100
Patients (n)	304	610
Enrollment date	2013–2017	2012–2017
Primary endpoint	Composite of all-cause death or HF hospitalization at 12 m	HF hospitalizations within 2 years of follow-up
Committee for eligibility	Local	Central
Crossover	Allowed	Not allowed
Follow-up	1 year	2 years
Inclusion criteria		
Aetiology of MR	Functional MR (ischaemic and non-ischaemic)	Functional MR (ischaemic and non-ischaemic)
MR severity degree	EROA >20 mm² or regurgitant volume >30 mL	EROA >30 mm² or regurgitant volume >45 mL
Prior hospitalization	At least one HF hospitalization	One HF hospitalization and/or BNP >300 pg/mL or NT-proBNP >1,500 pg/mL
NYHA class	II–IV despite optimal medical treatment	II-IV despite optimal medical treatment
LVEF	15–40%	20–50%
LVESD	Not required	<70 mm
Pulmonary hypertension	Included	Excluded SPAP >70 mmHg
RV dysfunction	Included	Excluded moderate-to-severe

Design and inclusion criteria. BNP, B-type natriuretic; EROA, effective regurgitant orifice area; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RV, right ventricle; SPAP, systolic pulmonary artery pressure.

31 *vs.* 41 mm²), more LV dilation (135 *vs.* 101 mL/m²), more advanced functional class (NYHA class III/IV: 69% *vs.* 60%), and higher right ventricular systolic pressure (54 *vs.* 44 mmHg) (13,14).

Medical treatment (Table 2)

In the COAPT trial, the optimal medical treatment was centrally assessed and only patients with maximum tolerated doses could be randomized (13). In the MITRA-FR trial, patients were evaluated by the local heart team with the lack of a central assessment to optimized medical treatment. Notably, changes in medical therapy in order to up-titrate were reported at follow-up in the COAPT trial (13). In the MITRA-FR this information has not been yet reported. In the MITRA-FR compare to COAPT, there was a higher rate of renin-angiotensin-aldosterone system blockers (84.7% *vs.* 67.1%) (13,14). In the COAPT trial, a higher use of these drugs was reported in the MitraClip group (71.5 *vs.* 62.8%) (13). In addition, there was an up-titration of medical treatment during the follow-up in the MitraClip group of the COAPT trial (13).

Transcatheter mitral valve repair procedure (Table 2)

The MitraClip procedure showed to be safe in both trials with low complication rates (13,14). In both trials, the MitraClip procedure was successful (91% in the MITRA-FR; and 95% in the COAPT). Regarding the rate of 1 *vs.* more than 1 MitraClip implanted was 46% in the

Table 2 MITRA-FR and COAPT trials

Features	MITRA-FR trial	COAPT trial
Patients' characteristics		
Age (years)	70	72
Male (sex)	74	64
LVEF	33.1	31.3
EROA (mm^2)	31	40.5
LVESD (mm)	–	53
LVEDV (mL/m^2)	135	101
RV systolic pressure (mmHg)	54	44.3
NYHA class III–IV	69	60
Diabetes mellitus	29.3	37.3
GFR ($mL/min/1.73\ m^2$)	49.6	49.3
Hypertension	–	80.4
Medical treatment		
Beta-blockers	89.5	90.3
ACEI or ARB or ARNI	84.7	67.1
MRA	54.8	50.1
Diuretics	98.6	89.1
Procedural outcomes		
Procedural success	95.8	98
Rate of 1 *vs.* >1 MitraClip	46	36
No MitraClip implantation	4.2	5
Acute MR 3+ or 4+	9	5
Tamponade	1.4	3

Patients' characteristics and procedural outcomes. Values are % or mean. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; EROA, effective regurgitant orifice area; GFR, glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RV, right ventricular.

MITRAFR *vs.* 36% in the COAPT (13,14). The proportion of patients with residual MR (3+ or 4+) immediately after procedure was less than 10% in both trials (13,14). The differences between ESC and ACC/AHA guidelines, related to the severity degree of MR and the missing echocardiographic information at 1-year follow-up in the MITRA-FR trial, did not allow performing reliable comparisons between trials regarding residual MR (4,5,14).

Results from the MITRA-FR and COAPT trials

First, primary efficacy endpoints differ between both trials (*Table 1*). The MITRA-FR used the composite of death and HF hospitalization at 1-year follow-up (14). The COAPT used a single endpoint of HF hospitalization at 2 years of follow-up (13). Notably, the COAPT trial was powered for secondary endpoints: mortality; and a composite of mortality + HF admissions at 1 and 2 years (13).

In the MITRA-FR trial, the mortality rates in the MitraClip group *vs.* the control group at 1-year follow-up were 24.3% *vs.* 22.4%. In the COAPT trial, the mortality rates in the MitraClip group *vs.* the control group at 1-year follow-up were 18.8% *vs.* 23.2%. The mortality rates at 2 years follow-up in the COAPT trial were 29% in the MitraClip group *vs.* 46% in the control group, HR: 0.62, P<0.001). Data about mortality rates at 2 years follow-up are not yet available for the MITRA-FR trial.

Role of imaging techniques in MR

The most widely used imaging technique to measure EROA, left ventricular volume, and LV function in patients with MR is the 2-dimensional echocardiography. However, the EROA may be overestimated by the proximal isovelocity hemispheric surface area (PISA) (3), Although 2-dimensional echocardiography is the most widely used imaging technique, it may underestimate LV volume; therefore, the use of ultrasound contrast could improve the accuracy of measurement of the LV volume and the endocardial borders (44,45).

Three-dimensional echocardiography is currently recommended for the measurement of the LV volume when there is a correct visualization of the endocardial borders. The use of the 3-dimensional transesophageal echocardiography in real-time is essential to guide the transcatheter mitral valve repair procedure, allowing to attempt the treatment of morphologically complex valves (6,7).

Conclusions

Some interesting characteristics should be highlighted. In the COAPT trial, the sample size was about 2-fold larger than in the MITRA-FR; the inclusion criteria were more demanding with the requirement of an optimal medical

therapy prior to randomization. However, the outcomes of the MITRA-FR and COAPT trials should be considered as complementary rather than contradictory. Before transcatheter mitral valve repair, it is necessary to assess the maximal optimization of medical treatment. The evaluation for the heart valve team, including specialists in HF, is essential in the decision-making process and the optimal management of the patient.

Transcatheter mitral valve repair with MitraClip seems to be safe and durable in patients with HF and moderate-to-severe functional MR who remained symptomatic despite maximally-tolerated optimal medical treatment. The MitraClip seems to reduce the rate of HF hospitalizations; and improve survival, quality of life and functional capacity in comparison to isolated optimal medical therapy. However, new medical treatments should be assessed and compared with invasive mitral valve procedures.

Notably, functional MR presents an active role in the progression of the cardiomyopathy. Thus, transcatheter mitral valve repair with MitraClip in selected patients, along the optimal medical therapy, may be able to break the mechanism, which leads to the end-stage disease in patients with chronic HF. In order to solve the doubts that may have generated the discrepancies between the COAPT and MITRA-FR trials, it is required better selecting the responders to functional MR correction; evaluating other percutaneous procedures (alone or in combination); as well as new medical therapies and comparing them with interventional procedures. Furthermore, large randomized trials with longer follow-up should be carried out to clarify the role of the transcatheter mitral valve repair in terms of prognosis in patients with HF.

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Footnote

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