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MitraClip treatment of *secondary* Mitral Regurgitation in Heart Failure with Reduced Ejection Fraction: Lessons and implications from Trials and Registries

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Abstract

Transcatheter mitral valve intervention using the MitraClip system has evolved as a new tool for the treatment of secondary mitral regurgitation (SMR) in patients with heart failure and reduced left ventricular ejection fraction (HFrEF). The purposes of this paper are, first, to review the pathophysiological mechanisms underlying the onset of SMR within the context of HFrEF progression; secondly, to reconcile the results from MitraClip randomized clinical trials and "real-world" registries, in order to highlight in a patient-based strategy the most relevant clinical predictors of favorable outcome after MitraClip implantation. The final goal is to identify the phenotype of the "ideal" patient and the most favorable timing for MitraClip treatment of SMR within the broad spectrum of HFrEF presentation.

Keywords: MitraClip; secondary mitral regurgitation; heart failure; patient selection; transcatheter mitral valve intervention.

Introduction

Secondary (or functional) mitral regurgitation (SMR) due to dilatation and spherical remodeling of the left ventricle is a common finding in chronic heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF) (HFrEF)[1,2]. When present it worsens the prognosis of these patients, even after effective surgical valve repair[3,4]. Moreover, in patients with SMR surgical outcomes are inferior to those of patients treated for primary (degenerative) mitral regurgitation (MR), and the candidacy for and the timing of SMR treatments remains controversial. Given the paucity of evidence, current ESC/EACTS and AHA/ACC[5,6] provide only a Class IIb indications for isolated surgical treatment. According to this and to their clinical status or presence of co-morbid conditions, only a small portion of patients with SMR are surgical candidates[7]. In this setting, minimally invasive techniques for mitral valve repair can play a vital role.

Percutaneous mitral valve repair using the MitraClip system (Abbott Vascular, Santa Clara, CA) has evolved as a new tool for the treatment of high-risk patients with HFrEF and concomitant SMR. Emerging evidence from several observational studies and randomized clinical trials has shed light on the feasibility, safety and effectiveness on HF symptoms reduction of MitraClip treatment in this setting[8-10]. Prominent among these studies are the COAPT[11] (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial and the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial[12,13].

The COAPT trial has shown for the first time that a device-therapy plus guideline-directed medical therapy (GDMT) can improve the survival of HF patients by reducing SMR compared to GDMT alone[11]. These results are in contrast with the findings reported by the MITRA-FR trial[12,13], that did not identify any difference in term of death or unplanned hospitalization between the two treatment groups. Given the conflicting data surrounding treatment of patients with SMR, the aim of this

paper is firstly to review the pathophysiological mechanisms underlying the onset of secondary MR and HF progression, and secondly to help identify the ideal candidacy and timing for percutaneous mitral valve repair in HFrEF spectrum by summarizing data from MitraClip randomized clinical trials and "real-world" registries.

Discussion

Secondary mitral regurgitation and HFrEF: *the "Vicious Circle"*

In patients with early HFrEF, LV chamber dilatation, increased MV annulus dimensions and papillary muscle displacement (and possibly dysfunction) lead to functional alteration of the MV apparatus, resulting in the development of SMR[14,15]. Consequently, the left ventricle undergoes an adaptive dilatative remodeling in order to accommodate the volume overload due to valvular regurgitation. As a result, myocardial contraction force increases as preload increments in accordance with the Frank-Starling law[16]. This phenomenon allows to maintain an appropriate emptying of the enlarged left ventricle and to preserve stroke volume and cardiac output (**Figure 1**). During this early phase, both surgical and percutaneous MV interventions may reduce the burden of volume overload on the struggling ventricle, reversing or delaying further LV dilatation and dysfunction (as observed in the COAPT trial[11]), ultimately improving symptoms and even survival. With the progression of the disease, the worsening of SMR and the increment of volume overload, patient can develop atrial fibrillation (AF) secondary to left atrium dilatation and remodling, while LV and annular dilation increase. All this leads to increased leaflets tethering and decreased closing forces, perpetuating the vicious cycle in "*valvular* HFrEF"[1,17]. The persistent volume overload increases LV diastolic wall stress leading to a reduction of myocardial contraction and cardiac output by multifactorial mechanism including impaired length–tension relationship[18], deficient excitation–contraction coupling[19] and adverse ventricular interdependence[20].

Finally, at this stage, recurrent cardiac decompensations characterize the clinical history of the patients identify a condition known as "*advanced* HFrEF". Any kind of intervention at this point

may be somehow effective on symptoms without improving survival. In order to break this vicious circle, we should define the proper time to perform MitraClip implantation in patients with SMR.

Evidence from RCTs and Registries: the results are more complementary than competitive

Nowadays, randomized clinical trials (RCTs) are considered essential to direct guidelines-derived decision-making process. Notwithstanding, RCTs do not address all relevant clinical questions and the results can be limited in generalizability. Registries try to fill this gap and have significant value in validating real-world use of a given therapy (effectiveness) because of the large number of patients treated in routine practice and the broad spectrum in patient selection. Therefore, RCTs and registries, with their strengths and limitations, are more complementary than competitive and the synergistic use of their results will be necessary to identify the most appropriate patient-based strategies for percutaneous mitral valve repair in the broad spectrum of HFrEF.

MITRA-FR and COAPT trials.

Two randomized clinical trials were specifically designed to test the hypothesis that treatment of significant SMR by transcatheter edge-to-edge mitral valve repair with the MitraClip device would improve outcomes. Data from the two trials show divergent results up to 2-year of follow-up. In the MITRA-FR trial[12,13] (304 patients), no statistically significant difference was found between the MitraClip treatment group compared to GDMT group regarding the primary composite endpoint of all cause death and first unplanned HF hospitalization up to "2-year" (63.8% and 67.1%, respectively)[13], or for rates of unplanned HF re-hospitalization alone (55.9% vs. 61.8%, respectively). In the COAPT trial[11] (614 patients), MitraClip treatment compared to GDMT alone resulted in significantly lower rates of "2-year" HF re-hospitalization (primary endpoint) (35.7% vs. 56.7%, respectively) and death from any cause (29.1% vs. 46.1%, respectively), and better quality of life and functional capacity.[11,21] In the MITRA-FR trial, the 1-year cardiovascular death rate was

unusually high in both groups (21.7% intervention group and 20.4% control group) compared to that observed previously in the largest real-world MitraClip registries including only SMR patients, **Table 1,** and near to that observed in the COAPT trial but at "2-year" follow-up (23.5% intervention group and 38.2% control group).[22]

Potential clinical explanations have been suggested to explain these contradictory results, which include differences in inclusion criteria, number of patients treated, baseline medical therapy and immediate procedural results. In the COAPT trial, the strict application of the inclusion and exclusion criteria, especially the achievement of maximally-tolerated GDMT before randomization, lead to a very slow enrolment of patients, obtaining a study population on optimal GDMT that count a 42% and 44% of patients without any HF hospitalization within 1-year before randomization in the device and control group respectively (that might suggest a condition of "early" HF). Furthermore, patients with evidence of right-sided congestive HF with echo evidence of moderate or severe right ventricular (RV) dysfunction were not included in the study. On the other hand, in the MITRA-FR trial, the randomization included all HF patients (with LVEF between 15%-40% and NYHA class II-IV) in which medical therapy was not been titrated to maximally tolerated before randomization. Instead, the echocardiographic data give us more objective comparison between the two trials. First, different definitions of severe SMR were used in both trials, according to the 2017 ACC/AHA[6] (COAPT trial) and the 2012 ESC/EACTS[5] (MITRA-FR trial) guidelines: in the COAPT study a regurgitant volume >60 mL/beat or an effective regurgitant orifice area (EROA) >40 mm² defined SMR as severe, while in the MITRA-FR study severe SMR was characterized by a regurgitant volume >30 mL/beat or an EROA >20 mm². According to that, in the COAPT trial the overall baseline MR grade was more severe than that reported in the MITRA-FR. In fact, 41% of COAPT patients had baseline EROA >40 mm^2 compared to only 16% of MITRA-FR patients. On the contrary, an EROA <30 mm^2 was present only in 14% of COAPT compared to 52% of MITRA-FR patients. Therefore, disagreement between the two guidelines definitions of severe SMR not only conveys a source of uncertainty for treating

physicians but might have affected the results of the two trials. As previously shown, the association between the respective cut-offs of EROA and regurgitant volume and mortality appears to be different[23], with a better relation to mortality for the cut-offs used in the COAPT trial to define SMR as severe[23].

Secondly, COAPT patients had lower indexed left ventricular end-diastolic volume (LVEDVi) compared to MITRA-FR patients (101±34 mL/m^2 vs. 135±35 mL/m^2, respectively) which is indirect sign of less LV negative remodeling.

According to these clinical and echocardiographic differences, we could interpret the conflicting results of the two trials as follows: MitraClip treatment of patients with advanced HF and moderate or moderate-to-severe SMR (as with most patients from the MITRA-FR trial) may not be effective; on the contrary patients with "early HF" (mild LV dilatation, none or few hospitalization for heart failure) and severe SMR (EROA >40 mm^2) are more likely to be the ideal ones to be treated with MitraClip therapy as observed in the COAPT trial. Our observations are in line with the concept of EROA/LVEDV ratio as a marker of "disproportionate" or "proportionate" MR, recently reported[24]. Accordingly, the COAPT enrolled patients with "disproportionate" MR (indicating patients with disproportionately large degree of MR compared with the moderate degree of LV dilatation), in contrast, the MITRA-FR trial enrolled more patients with "proportionate" MR (which means that MR was related more to LV enlargement and chronic advanced HF than to a reversible defect in mitral valve leaflets coaptation). Of course, patients from MITRA-FR trial benefit less by surgical mitral valve repair, especially when the LV systolic dimensions are also increased[22]. Finally, we support the hypothesis regarding the fact that in the MITRA-FR the marked LV enlargement of that patients rather than the expertise of the operators was the main cause of the lower rates of procedural success not only during the follow-up but also at the end of the procedure[25].

Predictors of adverse outcome from Registries of MitraClip in secondary MR.

After more than 10 years of use in over than 80.000 patients worldwide, MitraClip in SMR is the most frequent indication (~60%). Substantial evidence on MitraClip effectiveness was obtained by

multicenter registries reporting significant symptomatic improvement[8], LV reverse remodeling[26] and reduction in HF re-hospitalization[27] during follow-up. Furthermore, some of these studies showed several baseline clinical, echocardiographic and laboratory predictors of unfavourable outcome after MitraClip treatment. In order to select the "ideal" HFrEF patient for MitraClip therapy, it is important to take into account a multitude of parameters. In **Table 2** are reported the most frequent baseline predictors of all-cause death at 1 or 2 years after MitraClip implantation, identified by relevant registries dealing with HFrEF patients with SMR[9,28-41]. Among these parameters, the following have greater risk of all-cause mortality after MitraClip: advanced HFrEF (NYHA class IV, NT-proBNP >10.000 ng/L), severe LV dysfunction (LVEF <25%), initial right ventricular dysfunction (TAPSE <15 mm, tricuspid regurgitation >2+). Moreover, acute procedural success (MVARC definition[42]) was identified as another main predictor of favourable outcome after MitraClip[34]. Interestingly, patients with advanced stage of the disease are very unlikely to have LV reverse remodeling after the MitraClip procedure despite achievement of sizable symptomatic improvement[43].

The "ideal" patient for MitraClip in HFrEF

Screening for the "ideal" patient for MitraClip treatment starts among symptomatic HFrEF patients with moderate-to-severe and severe SMR (≥3+; EROA >30 mm^2)[44] as a second step of treatment on top to GDMT, which must also include angiotensin receptor-neprilysin inhibitor (ARNI) and cardiac resynchronization therapy (CRT) if indicated. In low-moderate risk patients, surgical correction of SMR concomitant to myocardial revascularization and/or aortic valve replacement is indicated with different strength according to baseline LV systolic function (class of recommendation [COR] I or COR II)[5,6]. In patients with severe SMR without need of additional surgery (for CABG or aortic valve replacement), surgical risk needs to be evaluated, considering baseline Logistic EuroSCORE, patient's comorbidities and, most of all, Heart Team opinions. In non-high risk patients presenting with a preserved LV function, surgery may be considered (COR

II), even if a RCT comparing surgery to GDMT for SMR treatment has never been done. In *high surgical risk patients* (including non-responder to CRT population), MitraClip could be considered in addition to GMDT, if suitable from an anatomical and technical point of view. In light of the above considerations, we believe it is reasonable to suggest that patients with: a) symptomatic non-advanced HFrEF (NYHA class II/III), b) non-severely depressed LV systolic function (LVEF ≥25%), c) preserved LV volume d) preserved right ventricular function, without severe tricuspid regurgitation, and e) absence of severe chronic renal failure[45], should be the ones evaluated for MitraClip implantation. We also believe that the Heart Team need to include also HF specialists and cardiac anesthesiologists, all of whom are important to optimize patient selection, procedural performance, and follow-up care. Obviously, these clinical, echocardiographic and laboratory characteristics are merely indicative and not restrictive in selecting the "ideal" patients, which can benefit the most from MitraClip in HFrEF. Therefore, the simultaneously presence of all these criteria is not required. Palliative device-therapy has to be taken into account in advanced HF patients in which it may temporarily improve symptoms. In selected cases, MitraClip can be also considered as "bridge" to left ventricular assist device (L-VAD) implantation or heart-transplantation (HTPL)[43,46]. An algorithm for a better SMR patient's stratification and management is presented in **Figure 2**.

Appropriate timing for MitraClip in HFrEF

Traditionally, cardiac surgeons have been reluctant to operate patients with SMR, based on the concept of SMR being an innocent bystander, reflecting the severity of LV dysfunction. The COAPT trial gives evidences to support early treatment of severe SMR without waiting for severe LV dilatation. The advantage of successful treatment of SMR is supported by analysing the secondary endpoints of the COAPT in terms of Kansas City Cardiomyopathy Questionnaire, 6-minute walk test, NYHA class and MR severity[11,21], which highlight the benefit obtained after MitraClip implantation in term of quality of life and functional capacity. Furthermore, despite GDMT, the control group tended to get worse over time compared to the MitraClip group. This finding suggests "secondary" MR to not only be a marker of sicker LV, but also a driving force in the vicious circle of HF progression (as showed in **Figure 1**). Recently, in a cohort of patients under guideline-directed HF therapy, it was observed that the adverse prognostic impact of SMR on HF was predominant in a specific "*intermediate-failure"* sub-cohort of patients, identified by NYHA class II-III, moderately reduced LV function (LVEF 30–40%) and within the second quartile of NT-proBNP (871–2360 pg/mL),[47] which was an underrepresented target population in the MITRA-FR trial (approximately 30% of the enrolled patients).

Studies conducted on animal models investigating the effect of early and late MV repair in SMR, suggest a window of opportunity where early repair can reverse the otherwise progressive LV negative remodeling.[48,49] Consequently, in HFrEF patients an early percutaneous correction of severe SMR can provide an additive value to medical therapy, resynchronization therapy and coronary revascularization (in case of ischemic aetiology of DCM), taking a main part in the fight against LV remodelling and delaying the onset of irreversible LV damages (such as myocardial fibrosis). Therefore, it is important to define the procedure timing in order to act on a LV that has not been severely remodeled by the LV volume loading-dependent process to due severe MR. The final "goal" would be the selection of symptomatic patients with substantial but not too severe LV dysfunction, in absence of advanced HF, when prognosis is going to be determined not only by the

amount of muscle damage, and MR contribution is still relevant in terms of symptoms reduction and survival benefit. At the same time, we need to treat patients with severe MR (EROA of >40 mm^2) and with significantly increased pulmonary artery pressure or pulmonary artery wedge pressure. Perhaps, at this stage it may be also relevant to assess if the degree of MR is proportionate or disproportionate to the entity of left ventricular dilatation, according to the theory recently proposed[24]; despite this hypothesis has yet to be proven, its confirmation could be very useful to choose the best treatment strategy in this setting. In the MITRA-FR, the definition of severe SMR by an EROA of >20 mm^2 potentially includes patients for whom SMR has not yet become a driving force of disease progression, and the subgroup analysis suggests a trend toward efficacy of MitraClip above an EROA of 40 mm^2 (<20% of MITRA-FR enrolled patients). This suggest better clinical results in the latter whereas SMR is not only quantitatively relevant in absolute value, but it is greater than expected in relationship with LVEDVi.

Finally, it would be also important to derive more information from Magnetic Resonance Imaging analysis to better evaluate myocardial tissue in terms of fibrosis, scar and myocardial viability which can be helpful to monitor the outcome and better predict the process of left ventricle positive or negative remodeling independently from baseline LVEF or LVEDV[51,52].

In conclusion, percutaneous mitral valve repair of secondary MR in HFrEF patients requires a timely benefit-risk assessment. We suggest a patient-based strategies in order to identify those "*who should be treated"*, in time to interrupt the ongoing pathological process, and not "*who can be treated"* according to anatomic and technical eligibility. Different grading of baseline SMR, together with differences in population size, medical therapies, as well as in LV remodeling patterns and right ventricular function can explain the divergence between the results observed in the two trials. Different clinical scenarios and methods of investigation can lead to different results in the same field of research. Only a careful interpretation of the data allows to highlight the uniqueness of scientific results and to optimize the clinical indication for patients.

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Table 1. Comparison of baseline characteristics and clinical outcomes of Trials and most relevant Registries on MitraClip in secondary mitral regurgitation (SMR) patients.

	ACCESS-EU[8*] (N=393)	MITRA-FR[12,13] (Intervention group) (N=152)	COAPT[11] (Intervention group) (N=302)	MI-ZU-BR[40] (N=314)	EVEREST II[50] (N=616)
Age (years)	73±8.9	70.1±10.1	71.7 ± 11.8	69±16.5	73.3±10.5
Male gender	67.9%	78.9%	66.6%	77%	59.1%
Ischemic aetiology	NA	62.5%	61%	68%	NA
NYHA class III-IV	87.3%	63.1%	57%	100%	77.8%
LVEF (%)	NA	33.3±6.5	31.3 ± 9.1	30.8±10	43.2±11.7
MR Severity					
Moderate-to-Severe	39.5% †	38% ‡	49%[§]	16%†	58.1%‖
Severe	59% †	61% ‡	51%[§]	84%†	22.7%‖
Logistic EuroSCORE (%)	24.8±18.9	NA	NA	18.5±18	NA
EuroSCORE II (%)	NA	6.6 (3.5–11.9)	NA	10 (7-13)	NA
1-/2-year outcomes[#]					
All death	17%	34.9%	26.5%	20%	22.4%
Cardiovascular death	NA	31%	20.2%	14%	15.3%

Data are presented as percentages for categorical variables, mean value ± SD or median value (interquartile range) for continuous variables. LVEF = left ventricle ejection fraction; MR = Mitral regurgitation; NA = not available; NYHA = New York Heart Association.

* = Data regarding only patients with SMR.

† = Semiquantitative evaluation of mitral regurgitation by pulsed Doppler technic.

‡ = Quantitative evaluation of mitral regurgitation by PISA method; severe mitral regurgitation was defined as EROA >20 mm^2 and/or regurgitant volume >45 mL.

§ = Quantitative evaluation of mitral regurgitation by PISA method; severe mitral regurgitation was defined as EROA ≥30 mm^2 and/or regurgitant volume >30 mL.

‖ = Semiquantitative and quantitative evaluation of mitral regurgitation.

= Data regarding the COAPT and MITRA-FR trials refer to 2-year follow-up. The rate of the events refer to the basal number of enrolled patients.

Table 2. Baseline clinical, echocardiographic and laboratory predictors of 1- and 2-years all-cause mortality after MitraClip implantation.

	Clinical characteristics		Echocardiographic features			Laboratory examinations		
	NYHA class	Log EuroSCORE (%)	LVEF (%)	TAPSE (mm)	TR	NT-proBNP (ng/L)	proBNP (pg/mL)	creatinine (mg/dL)
TCVT[28]			**<30**					
GRASP[29]	**IV**		**<30**		**>2+**			
GRASP-IT[30]	**IV**							
TRAMI[9]	**IV**		**<30**		**>3+**			**≥1.5**
Paranskaya et al.[31]		**≥20**						
Neuss et al.[32]	**IV**			**<15**		**>10.000**		
Taramasso et al.[33]							**≥1.600**	
Puls et al.[34]	**IV**							
Boerlage-vanDijk et al.[35]					**≥3+**	**≥5.000**		
Kaneko et al.[36]				**<15**				
Godino et al.[37]		**>25**						
Schueler et al.[38]					**>2+**			
Jabs et al.[39]								**>2**

Godino et al.[40]	**≤25**	**≥10.000**
Osteresch et al.[41]	**≤16**	

LVEF = left ventricle ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; proBNP = pro–B-type natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

Figure titles and legends

Figure 1. The vicious circle of secondary mitral regurgitation (SMR) in heart failure with reduced ejection fraction (HFrEF) patients.

Figure 2. Algorithm for secondary mitral regurgitation (SMR) management in heart failure with reduced ejection fraction (HFrEF) and patient selection for MitraClip.

*ESC/EACTS/HFA Guidelines

§ACC/AHA/HFSA Guidelines

a = In patients undergoing CABG or AVR, ACC/AHA/HFSA Guidelines do not consider baseline LVEF in the therapeutic decision-making process for concomitant valvular surgery.

b = According to ACC/AHA/HFSA Guidelines, it is reasonable to choose chordal-sparing mitral valve replacement for chronic severe ischemic MR (COR IIa), whereas mitral valve repair or replacement may be considered for chronic severe secondary MR (COR IIb) in patients undergoing isolated mitral surgery.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; AVR = aortic valve replacement; CABG = coronary artery by-pass graft; COR = class of recommendation; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; HF = heart failure; HTPL = heart transplantation; LBBB = left bundle branch block; Log EuroSCORE = Logistic European System for Cardiac Operative Risk Evaluation; L-VAD = left ventricular assist device; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; SMR = secondary mitral regurgitation; TAPSE = tricuspid annular plane systolic excursion.

Figure 1

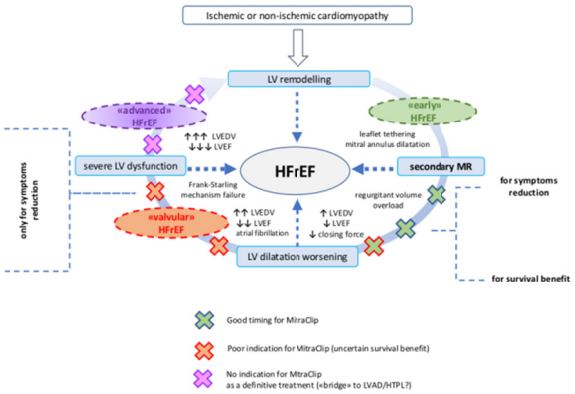

Figure 2