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Review Article

Percutaneous mitral valve repair by MitraClip: critical-comparative analysis of MITRA-FR and COAPT clinical trials

Reparo percutâneo de valva mitral pelo MitraClip: análise crítico-comparativa dos ensaios clínicos MITRA-FR E COAPT

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ABSTRACT: *Introduction*: Valvuloplasty is indicated as treatment for severe mitral regurgitation and the transcatheter technique is an option to thoracotomy. The MitraClip device for percutaneous mitral valve repair has been tested in two randomized clinical trials with conflicting results: MITRA-FR and COAPT. *Objective*: Analyze the methodological varieties presented by the trials. *Method*: Critical-comparative review between MITRA-FR and COAPT. *Results*: COAPT presented a 98% success rate and a reduction of the hospitalization rate for heart failure. On the contrary, MITRA-FR trial did not present any benefits when it comes to reducing the mortality rate or unplanned hospitalization for heart failure. *Discussion*: The selection of participants in COAPT was more rigorous. Although COAPT used a higher number of clips per surgery, the primary outcome in both trials was similar. In COAPT, medication follow-up was established by a committee, with a significant increase in the use of beta-blockers in the experimental group being reported. Furthermore, financial interests may have corroborated the results found in COAPT. *Conclusion*: The conflicting results presented by MITRA-FR and COAPT are explained by methodological differences, but the positive result presented by COAPT bears higher risk of bias.

Keywords: Mitral regurgitation; Minimally invasive surgical procedures; Clinical trial.

RESUMO: *Introdução*: A valvuloplastia é indicada para o tratamento de regurgitação mitral grave, sendo a técnica transcateter uma opção à toracotomia. Testou-se o dispositivo MitraClip para reparo percutâneo da valva mitral em dois ensaios clínicos randomizados com resultados antagônicos: MITRA-FR e COAPT. *Objetivo*: Analisar as variáveis metodológicas apresentadas pelos ensaios. *Método*: Revisão crítico-comparativa entre MITRA-FR e COAPT. *Resultados*: COAPT apresentou taxa de sucesso de 98% e redução na taxa de hospitalização por IC. Já MITRA-FR não demonstrou redução da taxa de mortalidade ou da hospitalização não planejada por IC em um ano. *Discussão*: A seleção de participantes em COAPT mostrou-se mais criteriosa. Embora COAPT tenha utilizado maior número de clipes por operação, o desfecho primário nos dois ensaios foi semelhante. No COAPT, o acompanhamento medicamentoso foi estabelecido por um comitê, sendo relatado aumento expressivo do uso de betabloqueadores no grupo experimental. Ademais, interesses financeiros podem ter corroborado para os resultados encontrados no COAPT. *Conclusão*: Os resultados conflitantes de MITRA-FR e COAPT são explicados por diferenças metodológicas, mas o resultado positivo apresentado por COAPT possui maior risco de viés.

Palavras-chave: Regurgitação mitral; Procedimentos cirúrgicos minimamente invasivos; Ensaio clínico.

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INTRODUCTION

Mitral regurgitation (MR) is the most common valve abnormality in the world and corresponds to the abnormal retrograde blood flow to the left atrium (LA) during systole, which compromises the body's hemodynamic balance[1].

It is estimated that MR is present in 19% of people with an average age of 54 years and in over 80% of elderly people aged 80 years or more. Mild/severe MR manifests itself in up to 12% of patients with acute myocardial infarction (AMI) within 1 month and in 15-30% of patients with congestive heart failure (CHF)[2].

MR-related etiologies are classified as primary or secondary. Primary MR results from anatomical changes in one or more components of the mitral apparatus, with rheumatic heart disease being the most common cause in Brazil[3]. In secondary MR, the mitral valve tracts and strings are usually normal or minimally thickened, being commonly observed in cases of left heart failure (HF) related to dilated or ischemic cardiomyopathies[4].

The reflux of blood caused by MR determines an increase in volume in the LA as well as in pressure, with subsequent dilation of the chambers. In addition, pulmonary venous hypertension may occur, causing pressure overload in the right ventricle (RV) and decreased myocardial contractility, which results in lower cardiac output and lower ejection fraction, thus characterizing HF[5].

In evaluating patients with MR, it is essential to determine the severity for an adequate therapeutic recommendation. Regurgitation severity can be measured under echocardiographic parameters, such as: Regurgitant Orifice Area (ROA), Regurgitant Volume (RVol) and Regurgitative Fraction (RF). Other comorbidities of the patient, hemodynamic consequences, stage of the disease and access to treatment should also be considered[6].

In cases where valvuloplasty is recommended for the treatment of severe or moderate secondary MR, the traditional approach is thoracotomy. This surgery, despite being able to mitigate symptoms and improve the quality of life, does not increase the survival rate. Therefore, the high prevalence of this condition in elderly patients with various comorbidities called for changes. Given this scenario, transcatheter techniques for percutaneous MR repair were developed, while ensuring a minimally invasive approach[6].

MitraClip is a device developed by Abbott Laboratory in California (USA) for performing percutaneous mitral valve reconstruction in patients with severe secondary MR. The lead catheter is introduced via a transfemoral venous route and guided through echocardiography to the LA[7].

The effectiveness of MitraClip was tested in two randomized clinical trials: MITRA-FR (*Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation*) and COAPT (*Transcatheter Mitral-Valve Repair in Patients with Heart Failure*).

The COAPT clinical trial was conducted at 78 sites across the United States and Canada with 614 patients diagnosed with moderate to severe HF and MR. The study showed rates of success and absence of significant complications as well as a reduction in the rate of hospitalization due to HF[8].

MITRA-FR clinical trial was conducted in France and included 304 patients with severe secondary MR, LV ejection fraction between 15 and 40%, and symptomatic HF. The study did not demonstrate any benefits associated to decreased mortality rate or unplanned hospitalization for HF[9].

In summary, the studies published by *The New England Journal of Medicine* in 2018, COAPT and MITRA-FR, presented conflicting results. Thus, the aim of this article is to analyze the methodological varieties between MITRA-FR and COAPT, with views to understanding the antagonistic results.

METHOD

This is a critical-comparative review between the MITRA-FR and COAPT clinical trials. The methodological model, the primary and secondary outcomes, the profile of patients undergoing the procedure and the number of devices implanted in the surgeries were compared.

After verifying the results, the criteria for selecting the participants, the technique used to carry out the surgeries, the medication follow-up and the sources of funding for each study were evaluated.

RESULTS

The criteria analyzed for the comparison between COAPT and MITRA-FR studies were: the primary and secondary outcomes, the number of devices implanted in the surgeries, the profile of patients undergoing the procedures and the methodological models (Table 1).

Table 1. Comparison between COAPT and MITRA-FR

	MITRA-FR	COAPT
Procedures conducted	94	97
Success rate (%)	95,8	98
Complication rate (%)	14,6	8,5
Primary and secondary outcomes		
Short-term effectiveness: reduction to MR 2 or < (%)	91	95
Long-term effectiveness: MR 2 or < (1 yr after MitraClip) (%)	83	95
Failure: Moderate to severe MR ≥ 3 following MitraClip (%)	9	5
Mortality in 12 months (control group)	22,4	23,2
VDFVE variation after 1 year (control group)	+7ml	+7ml
VDFVE variation after 1 year (experimental group)	-2ml	-5ml
Implanted devices (%)		
1 clip	46	36,2
2 clips	45	53,6
3 clips	9	7,9
4 clips	0	0,3
Information on the patients		
Number of patients	304	614
Average age	70	72
Selected/enrolled patients	304/452	614/1576
Cardiac Morphophysiology		
Average LVEF (%)	33,1	31,3
Average ROA (mm^2)	31	40,5
Average LVFSV (mm)	-	53
Average LVFDV (ml/mm^2)	135	101
RV Average Systolic Pressure (mmHg)	54	44,3
HF Classification – NYHA Class (%)		
II	32,8	38,9
III	58,5	52,4
IV	8,5	8
Other comorbidities		
Diabetes (%)	29,3	37,3
Hypertension (%)	-	80,4
Ischemic history (%)	59,4	60,7
Average GFR ($ml/min/1,73m^2$)	49,6	49,3
Previous Hospitalization for HF (<1 year)	100	57,1
Use of medication (%)		
Beta blockers	89,5	90,3
ACEI, ARB or NARI	84,7	67,1
MRA	54,8	50,1
Diuretics	98,6	89,1
Study models		
Study Design	Prospective, randomized	Prospective, randomized
Duration (months)	40	57
Randomization (experimental/control)	152/152	302/312
Experimental group	TMOD + MitraClip	TMOD + MitraClip
Control group	GOMT	GOMT
GOMT	Variable adjustment through clinical assessment by the local medical team.	Maximum stable doses determined and optional use of cardiac resynchronization therapy.
MR severity definition	European Guidelines ROA EROA > $20mm^2$ or RV > 30 ml/beat	North-American Guidelines ROA EROA > $30mm^2$ or RV > 45 ml/beat
Previous hospitalization and BNP	At least one hospitalization for HF in 12 months. BNP not required.	At least one hospitalization for HF in 12 months and/or BNP> 300 pg/ml or BNP Pro N-t > 1500 pg/ml.
Right ventricular dysfunction and pulmonary hypertension	Included	PASP excluded > 70 mmHg and moderate or severe right ventricular dysfunction.
Eligibility committee	Assessment by the local cardiac team.	Assessment by the local cardiac team and the eligibility committee.
Funding	Ministry of Health and National Research Program of France	Abbott Vascular
Exclusion criteria	Renal replacement therapy, severe liver failure.	Stage D heart failure, COPD with home oxygen or oral steroids, clinical signs of right heart failure and moderate or severe right ventricular dysfunction, modified Rankin scale ≥ 4 (moderate to severe disability).
Primary Endpoint	Includes all causes of death or unplanned hospitalization for HF within 12 months	HF hospitalizations within 24 months of follow-up and no device-related complications over the 12-month follow-up period

LEGEND: LVEF: Left Ventricle Ejection Fraction; ROA: Regurgitant Orifice Area; LVFSV: Left Ventricle Final Systolic Volume; LVFDV: Left Ventricle Final Diastolic Volume; GFR: Glomerular Filtration Rate; ACEI: Angiotensin Conversion Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; NARI: Neprilysin and Angiotensin Receptor Inhibitor; MRA: Mineralocorticoid Receptor Antagonists; NYHA: New York Heart Association; GOMT: Guideline-Oriented Medical Therapy; BNP: B-type Natriuretic Peptide; PASP: Pulmonary Artery Systolic Pressure; ROA: Regurgitant Orifice Area; NT-pro BNP: B-type Natriuretic Peptide Prohormone N-Terminal; COPD: Chronic Obstructive Pulmonary Disease; HF: Heart Failure; MR: Mitral Regurgitation.

DISCUSSION

MITRA-FR and COAPT studies showed conflicting results on the effectiveness of percutaneous mitral valve repair by MitraClip: MITRA-FR showed a negative result while COAPT presented a positive one.

COAPT study evidenced a 98% success rate, a no-device-related complication rate of 96.6%, as well as a lower hospitalization rate for HF. MITRA-FR clinical trial, in turn, did not demonstrate any benefits associated to reduced mortality rate or unplanned hospitalization for HF within one year, when comparing the control and experimental groups.

In MITRA-FR, 83% of the patients had MR at a degree less than or equal to two, after 12 months. In COAPT, this percentage was 95%. Rates of procedural complications, such as device implant failure, cardiogenic shock, and tamponade, were found to be higher in MITRA-FR.

Given this scenario and according to the principle of compliance of Evidence-Based Medicine, once a benefit is proven, it shall be reproducible for a wide range of patients, unless the patients selected for the study have very specific and discordant characteristics. In the case of COAPT and MITRA-FR, the selected patients do not have the same characteristics, which would justify the divergent results and allow the determination of the specific group of patients who would benefit from the MitraClip device[10]. However, other biases can be identified in the study design.

Thus, after making an objective comparison between MITRA-FR and COAPT (Table 1), four main parameters were evaluated: the selection of participants, the technique employed to carry out the surgery, medication follow-up and the sources of funding.

Selection of participants

The first point of divergence in patient selection concerns the use of different guidelines to classify the severity of MR, even though both trials have considered severe secondary MR as an eligibility criterion. MITRA-FR was based on the guidelines of the European Society of Cardiology - *European guidelines for the management of heart valve diseases"* (2012), which defined as severity factors for MR the ROA greater than or equal to 20mm^2 and/or the regurgitant volume greater than or equal to 30 mL. COAPT was based on the guidelines issued by the American Heart Association for the treatment of patients with valvopathy (2006/2008), which determined the ROA to be greater than or equal to 30mm^2 and the regurgitant volume greater than or equal to 45mL[11].

In addition, the COAPT study had a significant proportion of patients enrolled and considered ineligible. In COAPT, the proportion of ineligible patients corresponded to 61%, while in MITRA-FR it was 32%. This difference is related to the eligibility criteria in the COAPT study, as patients were evaluated by a central selection committee responsible for determining prerequisites[12]. Therefore, the profile of the individuals selected by COAPT is not similar to the profile of patients who show up in doctors' offices with complaints related to moderate/severe secondary MR, which suggests a selection bias.

Regarding the patients who underwent the procedure, an analysis of the baseline status of COAPT and MITRA-FR participants indicates the presence of two distinct groups. Patients who joined the MITRA-FR clinical trial showed a higher degree of LV impairment when compared to COAPT patients.

In MITRA-FR, the LV diastolic dimension of 70% of the patients was greater than 65mm, while in the COAPT, those with a diastolic dimension greater than 70mm were excluded. MITRA-FR patients, despite having higher left ventricular dilatation than those of COAPT, had it proportionally to the remaining cardiac chambers[11].

MITRA-FR patients had an average of 252ml end-diastolic volume in the LV and 31 mm^2 for the ROA. On the other hand, COAPT patients exhibited an average of 192ml of LV final diastolic volume and 41mm^2 of ROA, indicating a disproportionately higher degree of MR when compared to the degree of enlargement of the LV chamber. Thus, COAPT patients had a ROA approximately 30% higher than MITRA-FR patients and their left ventricular volumes were approximately 30% lower, indicating the degree of disproportionality of the LV[11].

The disproportionate LV indicates less impairment of this cardiac chamber when compared to the others. In this case, the root of the problem could be on the valve and not on the ventricular apparatus, a characteristic that was observed in the participants selected for COAPT.

The left ventricular ejection fraction was also discrepant among the participants of the trials. While this fraction ranged between 15 and 40% in MITRA-FR, in COAPT it was between 20 and 50%[11].

Surgery technique

Regarding the technique, in COAPT a higher number of clips per surgery was implanted, which can be justified by the use of 3D images. 3D images make it easier to identify leaks around the mitral valve, thus requiring more clips to be implanted[12].

However, the analysis of the number of clips to be implanted is subjective, since each patient is in a different stage of HF. Therefore, to propose that the discrepancy between the results is justified by the technique alone would be to question the French medical practice in MITRA-FR, while suggesting that North American physicians, in COAPT, made better judgment when deciding on the number of clips to be used.

It is noteworthy that the primary outcome in the two

trials was similar, with residual MR following the procedure being less than 10% in both. Nevertheless, in one year of follow-up, 17% of the patients who had undergone MITRA-FR showed moderate to severe (3+) residual MR, whereas in COAPT this occurred in only 5% of the patients[10].

Medication follow-up

Regarding medication follow-up, it is necessary to highlight that the patients were already using drugs to control HF in both studies.

In COAPT, a guideline-oriented medical therapy (GOMT) was adopted, which required consideration before the intervention[13]. Furthermore, a specific committee was set up for the systematic assessment of patients throughout the study and due adjustment of the administered drugs. In MITRA-FR, the evaluation of drug therapy was carried out individually by each service center linked to the study, with no specific standardization[13].

In the COAPT study, a significant increase in the use of beta-blockers was reported for the group undergoing the procedure, when compared to the control group, due to higher blood pressure following MitraClip implant. However, it is worth highlighting that in open studies there is a tendency for post-procedural patients to receive more attention than those who did not undergo it, which configures a performance bias.

Funding

MITRA-FR trial was funded by the Ministry of Health and National Research Program of France, comprising a limited budget when compared to COAPT, which in turn was sponsored by Abbott - manufacturer of the MitraClip system.

In this sense, the budget difference is reflected in a more thorough study design, both in relation to the selection of patients and when it comes to specialized therapeutic follow-up, for example.

Moreover, financial interests related to the MitraClip System can interfere with the objectivity of the results, creating a publication bias and compromising the levels of evidence in the study.

CONCLUSION

The conflicting results presented by MITRA-FR and COAPT are explained by methodological differences. However, the positive result presented by COAPT bears a higher risk of bias than the negative result presented by MITRA-FR. Accordingly, the level of evidence for MITRA-FR result is more reliable and more widely applicable to patients with moderate/severe secondary MR present in Cardiology offices.

Other randomized trials aim to test the effectiveness of MitraClip for the treatment of MR and are promising to confirm or not COAPT results. The Reshape-HF2 study, for instance, carried out in nine countries in Europe, is forecast to be completed in 2021.

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