Rev Esp Cardiol. 2019;72(12):994–997

Editorial

Importance of the Left Ventricle in Secondary Mitral Regurgitation. Hunt With Cats and You Catch Only Rats

La importancia del ventrículo izquierdo en la insuficiencia mitral secundaria... Dime con quién andas y te diré quién eres

Juan Manuel Monteagudo Ruiz and José Luis Zamorano Gómez*

CIBERCV, Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Madrid, Spain

Article history:
Available online 3 September 2019

The aging population and the increasing survival of patients with ischemic heart disease has resulted in an increased prevalence of secondary mitral regurgitation (MR).[1] Up to a quarter of patients with heart failure (HF) with reduced systolic function develop severe MR, and the presence of significant MR in these patients has been associated with increased morbidity and mortality.[2,3]

The approach to patients with secondary MR is complex. The morbidity and mortality of patients with ventricular dysfunction and significant MR remain high despite medical treatment.[4] Beyond medical treatment, the role of isolated surgery for secondary MR is controversial. Firstly, the results of surgery for secondary MR are poor.[5,6] Secondly, due to ventricular dysfunction and other comorbidities, a large proportion of these patients have a high surgical risk and are not candidates for intervention. In practice, few patients with secondary MR undergo surgery for the mitral valve alone.

The reality of the poor prognosis despite standard treatment and the high proportion of patients who are not candidates for intervention despite being symptomatic have made the approach to secondary MR one of the most pertinent unmet needs in cardiology.

In an attempt to address this need, percutaneous mitral valve devices have been created in the last decade. The most widely used device worldwide is the mitral clip (MitraClip, Abbott Vascular, Inc; Santa Clara, California, USA). EVEREST II demonstrated that the device was less effective at reducing MR, but was safer than conventional surgery.[7] Most of the patients had primary MR and a low surgical risk. However, in subsequent years, in Europe, the MitraClip has generally been used in older patients with high surgical risk and secondary MR.[8,9] Until now, this practice has been based on favorable outcomes from observational studies and the lack of any real alternative.

An important qualitative advance was made in 2018 with the presentation of the first 2 randomized clinical trials on the percutaneous treatment of secondary MR: MITRA-FR[10] and COAPT.[11]

The publicly-funded MITRA-FR trial included 304 patients with severe secondary MR (defined as an effective regurgitant orifice area [EROA] $>$ 20 mm^2 or a regurgitant volume $>$ 30 mL), a left ventricular ejection fraction (LVEF) of between 15% and 40%, and symptomatic HF. Patients were randomized into 2 groups: in the first, patients received percutaneous mitral valve repair in addition to medical treatment, and in the second, they received medical treatment only. The primary outcome was a composite of death from any cause and admissions for HF at 1 year. The study found no significant differences in the primary outcome between the 2 groups (54.6% in the intervention group and 51.3% in the control group; odds ratio [OR] = 1.16; 95% confidence interval [95% CI], 0.73-1.84); P = .53).

The COAPT trial, funded by Abbot Vascular, included 614 patients with severe secondary MR (defined as an EROA $>$ 30 mm^2 or a regurgitant volume $>$ 45 mL), an LVEF of between 20% and 50%, and symptomatic HF despite optimal medical treatment. The patients were randomized into 2 groups similarly to the MITRA-FR trial. The primary outcome was admissions for HF at 2 years. The study found a significant reduction in hospital admissions (35.8% per patient-year in the intervention group and 67.9% per patient-year in the control group; hazard ratio [HR] = 0.53; 95% CI, 0.40-0.70; $P < .001$). It also found significant differences in the overall mortality between the 2 groups (29.1% vs 46.1%; HR = 0.62; 95% CI, 0.46-0.82; $P < .001$) and in other secondary outcomes such as MR severity, quality of life, 6 minute walk test, functional class, and ventricular volumes.

These diametrically opposed findings raise the following question: how do we explain such apparently contradictory results?

Both trials randomized patients to MitraClip along with best medical treatment vs best medical treatment alone. The MITRA-FR trial found no differences in the composite outcome of death and admissions for HF at 1 year, while the COAPT trial found a significant reduction in hospital admissions for HF at 2 years (primary outcome) and death (secondary outcome). Since the publication of the 2 studies, this point has been widely debated.[12,13] Although both had the same outcome measure, there were clear differences in terms of patient selection, optimization of medical treatment, and study design.

* Corresponding author: Servicio de Cardiología, Hospital Ramón y Cajal, Ctra. de Colmenar Km 9.100, 28034 Madrid, Spain.
E-mail address: zamorano@secardiologia.es (J.L. Zamorano Gómez).

https://doi.org/10.1016/j.rec.2019.08.003

DIFFERENCES BETWEEN MITRA-FR AND COAPT

Differences in the study design

As mentioned, the 2 studies had different primary efficacy outcome measures and follow-up times. The differences in mortality in the COAPT trial only occurred in the second year. However, the differences in hospital admissions between the 2 arms became apparent very early on, whereas in the MITRA-FR trial no significant differences were found at 1 year of follow-up. In addition, the follow-up was more rigorous in the COAPT trial, with data available for the 1-year follow-up for the vast majority of patients (97.7% of the intervention group and 94.2% of the control group). While the COAPT trial demonstrated an improvement in quality of life, functional class, and functional capacity, the MITRA-FR trial did not analyze these secondary outcomes due to a large amount of missing data at the 1-year follow-up.

Differences in medical treatment

In the COAPT trial, a central committee confirmed that the patients were on maximum doses of medical treatment. In the MITRA-FR trial, although there was no such centralized checking of doses, the percentage use of drugs was higher than in the COAPT trial. In the control groups, the percentage of patients on treatment with beta-blockers, angiotensin II converting enzyme inhibitors (ACE-I)/angiotensin II receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitors (ARNI) and aldosterone receptor antagonists were, respectively, 89.7%, 62.8% and 49.7% in the COAPT trial and 90.8%, 86.4% and 53% in the MITRA-FR trial. In addition, the baseline values of natriuretic peptides were lower in the MITRA-FR trial, which could indicate better-optimized treatment. IIn addition, in the COAPT trial, the baseline medical treatment was better in the intervention group than in the control group. Specifically, 71.2% of patients in the intervention group were on ACE-I/ARB/ARNI vs 62.8% in the control group. These differences increased over the follow-up period. While the 2 studies differed in treatment, these differences were probably not enough to explain the disparity in the results.

Procedural differences

Another explanation that has been put forward repeatedly relates to the difference in the results of the procedure from a technical point of view. Implantation of more than 1 clip was more common in the COAPT trial than in the MITRA-FR trial (63% vs 54%). In addition, the number of patients with significant residual MR after the procedure was higher in the MITRA-FR trial (8.1% vs 5%). In an unpublished subanalysis of the COAPT trial, the rate of admissions and overall mortality at 30 days was notably lower in patients with MR grade ≤ 2 compared with patients with grade 3/4 independently of whether they were in the intervention or control group. This indicates that the greater reduction in MR with the MitraClip than with medical treatment alone explains in large part the benefits of the device and shows the importance of aiming for the lowest possible residual MR. The reported complication rate in the MITRA-FR trial was also higher, but the difference in how complications were assessed makes it impossible to directly compare the 2 studies in this respect. Regardless of this consideration, the success rate in both studies was very high, and the complication rate was low, so these differences are insufficient to explain the discrepancies in the results.

Differences in patient selection

In the COAPT trial, the MitraClip had a highly beneficial effect. The number needed to treat was 3.1. The difference between this result and the neutral result of the MITRA-FR trial cannot be fully explained by the factors discussed above. The most plausible explanation is that the treatment was applied to very different populations. The existence of a central eligibility committee in the COAPT trial could have resulted in a highly selected population, whereas the MITRA-FR trial population may have been more similar to that of routine clinical practice.

The inclusion and exclusion criteria in the 2 studies differed substantially. The MITRA-FR trial included patients with an LVEF between 15% and 40%, while the COAPT trial included patients with an LVEF between 20% and 50%. All the patients in the MITRA-FR trial had had an admission in the previous year, while in the COAPT trial it was sufficient to have high levels of natriuretic peptides. The COAPT trial also excluded patients with a left ventricular end diastolic diameter of > 70 mm, patients with stage *D* HF, cardiomyopathy, significant right ventricular dysfunction, pulmonary systolic pressure > 70 mmHg, or severe chronic obstructive pulmonary disease, among other comorbidities. It has been postulated that the patient population in the MITRA-FR trial had more advanced disease and higher comorbidity, which could have resulted in treatment futility in many cases. However, we must exercise prudence: the all-cause 1-year mortality in the control groups in both studies were very similar: 23.2% in the COAPT trial and 22.4% in the MITRA-FR trial, a point that goes against the idea that the MITRA-FR population was a much sicker population.

Differences in the severity of mitral regurgitation

The above discussion would suggest that the main difference between the 2 populations relates to the MR itself. Quantification of secondary MR is highly complex. The proof lies in the sustained discrepancies between current European and American guidelines.[14,15] The European guidelines suggest a cutoff for severe MR of an EROA of 20 mm^2 and a regurgitant volume of 30 mL, while the American guidelines maintain the same cutoff as for primary MR, an EROA of 40 mm^2 and a regurgitant volume of 60 mL.

The various inclusion criteria used led to the 2 study populations differing in one key point: their MR. In the MITRA-FR trial, the mean EROA was 31 mm^2 with a mean regurgitant volume of 45 mL, while in the COAPT trial, the mean EROA was 41 mm^2 and the mean regurgitant volume was 60 mL. In addition, the patients in the MITRA-FR trial had more dilated left ventricles (end diastolic volume index of 135 vs 101 mL/m^2), probably because the COAPT trial excluded patients with very dilated ventricles (end diastolic diameter > 70 mm).

In summary, patients in the COAPT trial had more severe MR and less dilated ventricles than those in the MITRA-FR trial. A subanalysis that stratified the population of this study according to the EROA (G.W. Stone, unpublished data) found no significant differences in the patient subgroup with an EROA of < 30 mm^2, a

subgroup that represents the overall majority of patients in the MITRA-FR trial.

Grayburn et al., [16] suggest that our concept of secondary MR is probably oversimplified and that these patients, in reality, form a widely heterogeneous group. The authors propose distinguishing between MR that is proportionate to ventricular dilatation and that which is disproportionate. The patients in the MITRA-FR trial, with more dilated ventricles, represent a population in which the MR is proportional to the ventricular dilatation and is a consequence, not a cause, of the ventricular disease. Therefore, these patients would benefit from treatments aimed at reducing the ventricular volume, but less so from those aimed at reducing the regurgitation. The patients in the COAPT trial represent disproportionate MR, with higher regurgitant volumes for smaller ventricles, in which regurgitation would play a key role in the progression of the ventricular disease. These patients would be ideal candidates for interventions aimed at correcting the MR.

The unpublished data mentioned above, however, invite caution. The mean antegrade flow measured on Doppler was 51 mL and the mean regurgitant volume measured with the PISA method was 60 mL, which means a mean stroke volume of 111 mL. However, the mean ventricular volumes calculated using the biplane Simpson method (left ventricular end diastolic volume, 194 mL; left ventricular end systolic volume, 136 mL) allow us to estimate a mean stroke volume of 58 mL. The most likely cause of this discrepancy is the systematic underestimation inherent to the calculation of ventricular volumes from 2-dimensional echocardiography.[17] These imprecisions in quantitative calculations limit the conclusions that can be drawn when comparing volumes between the 2 studies and provide further evidence of the real difficulty involved in evaluating secondary MR.

IMPLICATIONS FOR CLINICAL PRACTICE

We propose that the results of the 2 trials should be interpreted as complementary rather than contradictory. The COAPT trial is the first randomized controlled trial that has demonstrated a benefit from the correction of secondary MR, suggesting that this may have an essential role in progression of myocardial involvement. A number needed to treat of 3 implies a benefit that cannot be ignored, especially when faced with a population for which both studies reported a total 1-year mortality of over 20% despite highly optimized medical treatment.

The MITRA-FR trial clearly shows the importance of proper patient selection. Even though the current data do not provide a definitive explanation for the discrepancy in the results, clinical practice must aim to reproduce the COAPT results by doing the following:

Patient selection should include those who have ventricular disfunction (LVEF $<$ 50%) and are symptomatic despite maximum tolerated doses of medical treatment and resynchronization therapy, when indicated. Decisions on patient selection should involve a team comprising cardiologists with expertise in heart failure, interventional cardiologists, and imaging experts.

To avoid treatment futility, patients should be excluded if they have very advanced disease (very dilated ventricles, New York Heart Association functional class IV, significant right ventricular dysfunction or advanced pulmonary hypertension) or significant comorbidities, such as severe lung disease.

A thorough evaluation of the MR must be performed. It is important to understand the limitations of 2-dimensional echocardiography and of the PISA method. Two-dimensional echocardiography tends to systematically underestimate left ventricular volume. The use of contrast echocardiography, 3-dimensional echocardiography, and cardiac magnetic resonance imaging may provide valuable additional information. As well as a thorough evaluation of the MR, a detailed study of the valve anatomy is essential, as this is a key determinant of the success of percutaneous repair. Patients should be excluded if their anatomy does not allow the possibility of optimal repair.

The procedure should be carried out in referral centers with a sufficient case load to ensure a high success rate and low complication rate. The aim of the procedure should be a residual MR $\leq$ grade 2, for which as many clips as considered necessary should be implanted.

The Reshape-HF2 trial (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation, NCT02444338), which is currently underway, will provide further data on the prognostic effect of the MitraClip in patients with secondary MR and enhance our understanding of this condition.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Monteagudo Ruiz JM, Galderisi M, Buonauro A, et al. Overview of mitral regurgitation in Europe: results from the European Registry of mitral regurgitation (EuMiClip). *Eur Heart J Cardiovasc Imaging.* 2018;19:503–507.
2. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart.* 2011;97:1675–1680.
3. García-Cosío Carmena MA, Roig Minguell E, Ferrero-Gregori A, Vázquez García R, Delgado Jiménez J, Cinca J. Prognostic implications of functional mitral regurgitation in patients with heart failure and reduced ejection fraction. *Rev Esp Cardiol.* 2017;70:785–787.
4. Agricola E, Ielasi A, Oppizzi M, et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail.* 2009;11:581–587.
5. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med.* 2014;370:23–32.
6. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med.* 2014;371:2178–2188.
7. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med.* 2011;364:1395–1406.
8. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol.* 2013;62:1052–1061.
9. Belen Cid AB, Rodríguez Leor O, Moreno R, Pérez de Prado A; Spanish Cardiac Catheterization and Coronary Intervention Registry. 27th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2017). *Rev Esp Cardiol.* 2018;71:1036–1046.
10. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med.* 2018;379:2297–2306.
11. Stone GW, Lindenfeld J, Abraham WT, et al. COAPT Investigators, Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318.
12. Estévez-Loureiro R. Debate: MitraClip. The interventional cardiologist perspective. *REC Interv Cardiol.* 2019;1:54–56.
13. Núñez J. Debate: MitraClip. The heart failure expert perspective. *REC Interv Cardiol.* 2019;1:51–53.
14. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739–2791.
15. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart

Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70:252–289.
16. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation. *JACC: Cardiovasc Imaging.* 2019;12:353–362.
17. Rigolli M, Anandabaskaran S, Christiansen JP, Whalley GA. Bias associated with left ventricular quantification by multimodality imaging: a systematic review and meta-analysis. *Open Heart.* 2016;3:e000388.