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Editorial

# Outcomes of MitraClip for functional mitral regurgitation: does the severity of left ventricular dysfunction matter?

## Resultados del MitraClip en la insuficiencia mitral funcional. ¿Influye la gravedad de la disfunción ventricular?

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Approximately 1 in 10 individuals aged ≥ 75 years has moderate or severe mitral regurgitation (MR).[1] The etiology of MR may be degenerative (or primary) or functional (or secondary). Functional MR (FMR) occurs as a consequence of annular dilatation and/or distortion of the subvalvular apparatus secondary to left ventricular (LV) remodeling from ischemic or nonischemic cardiomyopathy, and is associated with poor prognosis.[2] Guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy have been shown to improve symptoms, LV function and, in some patients, to reduce the severity of FMR. However, unlike degenerative (primary) MR where mitral valve surgery is often curative, surgical repair or replacement has not been shown to improve functional status or survival in patients with FMR.[3–5]

Recently, 2 randomized controlled trials, MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), evaluated the efficacy and safety of transcatheter edge-to-edge mitral valve repair with the MitraClip system (Abbott Structural, United States) in patients with ≥ moderate-to-severe FMR.[6,7] MITRA-FR demonstrated no significant difference in all-cause death or heart failure (HF) hospitalization at 1 or 2 years with MitraClip vs medical therapy alone.[6,8] In contrast, in the COAPT trial, MitraClip resulted in a significant reduction in HF hospitalizations as well as all-cause death at 2 years compared with GDMT alone.[7] Further, all secondary outcomes including New York Heart Association (NYHA) functional class and changes in the Kansas City Cardiomyopathy Questionnaire score, 6-minute walk test distance and LV end-diastolic volume from baseline to 12 months were in favor of MitraClip over GDMT alone.

The discrepant findings of MITRA-FR and COAPT can be explained in large part by the differences in optimization of GDMT, operator experience, degree of MR reduction, and severity of MR relative to LV function in the patients enrolled in these 2 trials.[9,10] In COAPT, medical therapy was optimized prior to randomization with only a few major changes in treatment during follow-up.[7] In contrast, in MITRA-FR medical therapy was not optimized in all patients at baseline and adjustments in medical treatment were allowed during follow-up to simulate "real-world" practice.[6] Further, the centers participating in COAPT had better periprocedural outcomes compared with MITRA-FR, including lower rates of procedural complications (8.5% vs 14.6%), lower rates of postprocedural MR ≥ moderate-to-severe at 1 year (5% vs 9%), as well as lower rates of residual MR ≥ moderate-to-severe (5% vs 17%), and may have possessed greater experience with the MitraClip device.[6,7] Last, while both trials enrolled patients with ≥ moderate-to-severe FMR, differences in definitions and thresholds of quantitative MR metrics and of LV ejection fraction (LVEF) led to patients enrolled in MITRA-FR having less severe MR and more LV systolic dysfunction ("proportionately severe MR"), whereas those enrolled in COAPT had more severe MR and less LV systolic dysfunction ("disproportionately severe MR").[10,11] Thus, in patients with FMR, MitraClip is of definite benefit in "COAPT-like" patients with ≥ moderate-to-severe MR (effective regurgitant orifice area [EROA], ≥ 0.3 $cm^2$ and regurgitant volume [RV], ≥ 45 mL) and mild-to-moderate LV systolic dysfunction (LVEF, ≥ 20% and LV end-systolic dimension [LVESD], ≤ 70 mm), and of no benefit in those with mild-to-moderate MR (EROA, < 0.3 $cm^2$ and RV, < 45 mL) and severe LV systolic dysfunction (LVEF, < 20% and LVESD, > 70 mm), or mild-to-moderate LV systolic dysfunction.[10] However, the usefulness of MitraClip in patients with ≥ moderate-to-severe MR and severe LV systolic dysfunction remains uncertain.

In a recent article published in *Revista Española de Cardiología*, Sanchis et al.[12] report the findings of a single-center retrospective observational study comparing the safety and efficacy of MitraClip in patients with ≥ moderate-to-severe FMR divided into 2 groups according to the degree of LV systolic dysfunction—poor LV (LVEF, > 20% and LV end-diastolic dimension [LVEDD], < 70 mm) and very poor LV (LVEF, < 20% and LVEDD, > 70 mm). Of 75 patients who underwent MitraClip implantation over a 6-year period, the first 10 were excluded to eliminate the possible influence of learning curve, and 7 additional patients with degenerative MR were excluded.[12] Fifty-eight patients with ≥ moderate-to-severe FMR who underwent MitraClip implantation were included in the study—28 (48.3%) with very poor LV and 30 (51.7%) with poor LV. The main outcome was freedom from HF hospitalization, heart transplant, or cardiovascular death. Other outcomes assessed were NYHA functional class, echocardiographic measurements, and HF hospitalizations before and 1 year after MitraClip implantation.[12]

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The mean age of the patients was 68.5 years and 25.9% were women.[12] There were no significant differences in the baseline characteristics between patients with very poor and poor LV. Mean LVEF, LVEDD, and LVESD in the very poor and poor LV groups was 22.2 vs 37.2%, 72.4 vs 57.9 mm, and 61.6 vs 41.1 mm, respectively.[12] The number of clips implanted was higher and procedure duration longer in patients with very poor LV. MR was reduced to $\leq$ 2+ in 94.8% of the patients, with no significant difference in the 2 groups. At a mean follow-up of 19.5 $\pm$ 13 months, freedom from HF hospitalization, heart transplant, or cardiovascular death was significantly higher in the poor LV group than in the very poor LV group (log-rank $P$ = .010).[12] At 1 year of follow-up, the proportion of patients in NYHA class I/II was significantly higher in both groups (84.4% vs 7.5% at baseline in the very poor LV group and 100% vs 3.4% at baseline in the poor LV group).[12] Similarly, compared with 1 year prior to implantation, rates of HF hospitalization were significantly lower 1 year postimplantation in both groups (11.1% vs 55.5% in the very poor LV group and 7.1% vs 46.4% in the poor LV group). Echocardiographic follow-up showed a sustained reduction in MR severity without significant differences between groups.

The authors should be congratulated on this important study.[12] Patients in the very poor LV group in the current study were similar to those enrolled in the MITRA-FR trial (mean LV end-diastolic volume, ~250 mL), but with worse LVEF and more severe MR (although the authors did not provide details of the quantitative echocardiographic criteria used to define MR severity, all patients in the very poor LV group had 4+ MR).[6,12] Although MitraClip implantation in the very poor LV group was associated with significant improvements in NYHA functional class and HF hospitalizations, Kaplan-Meier curves for the composite endpoint of HF hospitalization, heart transplant, or cardiovascular death demonstrated a significantly lower event-free survival of ~40% vs ~85% in the poor LV group at 2 years.[12] These findings are similar to results of the MITRA-FR trial, in which all-cause death or HF hospitalization occurred in 63.8% of the patients at 24 months.[8] Thus, it is likely that, despite having more severe MR, patients in the very severe LV group in the current study represent those with "proportionate MR", in which the events are driven mainly by the disease process in the LV and less so by the MR.[11]

In addition to the small sample size, retrospective design, and unmeasured confounding, an important limitation of the current study is the lack of a control group, ie, patients with very poor LV treated with GDMT alone. Although the authors compared HF hospitalizations and NYHA functional class 1 year before and 1 year after MitraClip implantation, they do not provide information on changes in medical therapy during this period.[12] Based on results of the MITRA-FR trial in which improvement in outcomes were seen in both the MitraClip and GDMT groups, it is possible that the authors may find no significant differences in functional status and/or event-free survival in patients with very poor LV who underwent MitraClip implantation compared with those receiving GDMT alone.[6,8]

Nonetheless, the study by Sanchis et al.[12] is an important step forward in understanding the role of MitraClip in patients with FMR and very poor LV function. Future studies should focus on determining the factors associated with improved outcomes with MitraClip in this group of patients to identify a potential subset of patients with proportionate MR who may still derive some benefit from MitraClip implantation.

## CONFLICTS OF INTEREST

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