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Editorial comment

Primary mitral regurgitation treated with transcatheter edge-to-edge repair. Does transthoracic echocardiography provide prognostic information?

Insuficiencia mitral primaria tratada con reparación percutánea de borde a borde: ¿aporta el ecocardiograma transtorácico información pronóstica?

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Mitral regurgitation (MR) is the second most common valve disease in Europe. The prevalence of moderate to severe forms is around 10% in persons older than 75 years, and the rate is on the rise. Therefore, MR can be considered a significant public health concern. Depending on the causal mechanism, MR can be categorized as primary (PMR) or secondary (SMR), which determines the treatment strategy to follow.[1] Management of PMR is based on the severity of the condition, the presence of symptoms, and the hemodynamic consequences on the heart chambers, with surgery being the most frequently indicated option. Nonetheless, surgical treatment of MR remains notably low. It is performed in only 29% of patients with severe PMR, mainly due to factors such as advanced age, the presence of comorbidities, and ventricular dysfunction, which contribute to a perceived high surgical risk.[2] This situation has led to the development of less invasive percutaneous treatment techniques in recent years. The most common among them is transcatheter edge-to-edge repair (TEER) with a mitral clip. However, only one randomized study comparing TEER to surgery has been published to date. The EVEREST II trial, including 279 patients with degenerative MR, reported a better safety profile with the percutaneous technique, but lower efficacy.[3] These results were confirmed at long-term follow-up,[4] leaving many questions unanswered. The COAPT trial demonstrated the benefit of adding TEER to medical treatment for selected patients with SMR due to left ventricular dysfunction,[5] but no randomized trial data are available for PMR. However, one recent study using a propensity score matching analysis in symptomatic PMR patients older than 65 years drawn from 3 major registries found that TEER was associated with better survival rates compared with the watchful waiting approach.[6]

Based on these data, current clinical guidelines recommend TEER (on an anatomically appropriate mitral valve) for PMR patients with severe symptoms and prohibitive surgical risk. However, it is only a class IIb recommendation, reflecting the uncertainty regarding the survival benefits of this treatment even in patients with no other therapeutic options.[1] The role of transesophageal echocardiography in selecting candidates for mitral TEER in PMR is widely recognized. The height and width of the leaflet eversion are the main prognostic factors for technical success.[2] Furthermore, certain echocardiographic findings obtained immediately after the procedure, such as mild or less severe MR and mean mitral gradient below 5 mmHg, indicate a favorable prognosis for mid-term clinical events.[7] However, there is little evidence regarding the prognostic significance of parameters acquired in this scenario with transthoracic echocardiography, a diagnostic tool available to all cardiologists referring patients for surgical or percutaneous treatment.

A recent article by Shechter et al.[8] published in *Revista Española de Cardiología* has shed some light on this question. It is a single-center, retrospective, observational study that analyzed the prognostic value of transthoracic echocardiography parameters for predicting clinical events at 1 year in patients with PMR treated by TEER. The primary outcome measure was a composite of all-cause mortality or hospitalization due to heart failure. In addition, the study evaluated the predictive capacity of the parameters in the presence of residual MR at 1 month and 1 year, and the functional class at 1-year follow-up. The data from 410 PMR patients undergoing TEER were analyzed. The patients had a high-risk clinical profile, with a median age of 83 (76-88) years and numerous comorbidities, including stage $\geq$ III chronic kidney disease in 76% and anemia in 58%. The condition had a degenerative etiology in 98.3% of cases, and more than 90% of patients were in New York Heart Association functional class III-IV. The median left ventricular ejection fraction was 63% (56%-68%), and tricuspid annular plane systolic excursion was 8 mm (15-22 mm). Pulmonary artery systolic pressure exceeded 50 mmHg in 39% of patients. As for medical therapy, certain comorbidities, such as anemia and chronic kidney disease could have led to some degree of undertreatment. Only 44% of patients were receiving oral anticoagulation (54% had atrial fibrillation or flutter) and 30% were not receiving loop diuretics despite the significant functional repercussions.

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Two features of interest can be derived from an analysis of the baseline characteristics of the study population. First, the patients exhibited an unfavorable clinical profile that could strongly be associated with the occurrence of the composite primary outcome, particularly all-cause mortality. This would hinder the performance of multivariate models based solely on the echocardiographic parameters. The MitraScore, a validated tool for predicting mortality in patients treated with TEER, includes certain clinical factors that were highly prevalent in this population, such as the aforementioned advanced age, anemia, and chronic kidney disease.[9] The second noteworthy feature is the similarity of this population to the patients included in another real-world study.[7] The profile of these populations differs considerably from that of patients in the EVEREST II trial, where, for example, less than one-third of the total were aged 75 years or older.[3] These differences underscore the importance of understanding the sample when analyzing prognostic factors or developing a prognostic model for use in clinical practice.

The combined outcome event of all-cause mortality or heart failure hospitalization within 1 year after the procedure occurred in 62 patients (14.9%). The 1-year mortality incidence was 8.5%, almost half the rate reported in the real-life study by Makkar et al.[7] (15.4%) and similar to the rate documented in EVEREST II[3] (6%), performed in a population with a more favorable clinical profile. The incidence of hospitalizations due to heart failure was 9%, similar to the 9.3% described by Makkar et al.[7] In the echocardiographic multivariate model, the only factor predictive of the combined event was left ventricular systolic diameter (LVSD) $\geq$ 2.1 cm/m^2 (hazard ratio = 2.44; 95% confidence interval, 1.09-4.68; P = .022), which was also associated with the outcome events separately. The prognostic significance of LVSD has been reported previously and incorporated into a predictive model for all-cause mortality or heart failure hospitalization based on data from the COAPT trial,[10] which, however, was conducted in patients with SMR. Although the clinical scenarios differ, these findings seem to highlight the prognostic role of LVSD in MR patients undergoing TEER treatment and encourage future research investigating the predictive capability of other markers of left ventricular remodeling in this specific context. Regarding the direct applicability of this parameter in clinical practice, it is essential to interpret the prognostic value of LVSD $\geq$ 2.1 cm/m^2 with caution until validated in subsequent studies. Nonetheless, LVSD is one of the original contributions of the study, and in other clinical settings, such as aortic regurgitation, it is a recognized predictor in guidelines. Therefore, the presence of a markedly dilated left ventricle should be considered together with other unfavorable clinical factors, such as advanced age and concomitant chronic kidney disease, when assessing the risk-benefits of TEER in PMR.

Atrial dilatation $\geq$ 60 mL/m^2 and tricuspid regurgitation at a level beyond moderate were associated with poorer functional outcomes (New York Heart Association III-IV) and the presence of residual MR greater than moderate at follow-up. Together with other factors, such as elevated pulmonary artery systolic pressure and ventricular dysfunction, the presence of tricuspid regurgitation at a level beyond mild was also an unfavorable risk factor in the COAPT score for SMR patients.[10] Taken together, these findings seem to emphasize the importance of avoiding delays in percutaneous treatment for symptomatic patients with PMR and an indication for TEER. According to the study by Shechter et al.,[8] patients in more advanced stages with greater deleterious modeling have a higher incidence of adverse events at follow-up, as well as poorer echocardiographic and functional results. In this study, parameters related to left ventricular systolic function, such as the left ventricular ejection fraction or the global longitudinal strain were not associated with unfavorable outcomes. However, the absence of associations between these and other echocardiographic factors could be due to limitations inherent to the study design, such as the sample size or missing values over follow-up.

The substantial recent advances in the field of structural interventions have led to the incorporation of a wide range of percutaneous procedures into routine practice, successfully treating many diseases, an achievement that was previously unimaginable. Nonetheless, these procedures are not without complications, and the incidence of adverse clinical events during follow-up cannot be disregarded.[11] To advance in the realm of precision medicine, it is essential to accurately identify patients who have a higher likelihood of benefiting from specific interventions and a low risk of complications and adverse events during follow-up. Clearly, studies such as that by Shechter et al.[8] are important to identify prognostic factors necessary for achieving these objectives without engaging in futile efforts. However, the applicability of event prediction based on a single factor is limited, as a patient's prognosis is naturally determined by multiple factors. Therefore, collective efforts are also needed to conduct studies with a sufficient sample size, allowing the development and validation of prognostic models that integrate individual factors into multiparametric models (clinical, imaging, and biomarkers) with sufficient predictive capacity to guide decision-making in clinical practice.

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CONFLICTS OF INTEREST

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