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EDITORIAL COMMENT

Mitral Regurgitation in Patients With Severe Aortic Regurgitation

When Misery Loves Company*

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Multiple valvular heart disease (MVHD) is highly prevalent (1). However, guidelines are still limited and mostly based on Level of Evidence: C reflecting the scarcity of data to support and guide clinical decision-making (2,3). This paradox is likely explained by the heterogeneity of these conditions in terms of combined pathogenesis, severity, surgical risk, reparability, and suitability for transcatheter therapies. The combination of mitral regurgitation (MR) and aortic regurgitation (AR) is a typical example of a relatively frequent but understudied MVHD. In this issue of the *Journal*, Yang et al. (4) deserve to be commended for their remarkable study aiming to address this knowledge gap by investigating the prevalence, mechanisms, etiologies, and survival impact of coexistent significant MR in severe AR.

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When AR is severe, any degree of MR may substantially increase left ventricular (LV) pre-load, resulting in LV dilation and dysfunction that may be even worse than that in isolated lesions (5). Moreover, MR enhances the downstream impact of AR through volume and pressure overload of the left atrium, predisposing patients to atrial fibrillation, pulmonary hypertension, and eventually, right ventricular dilatation and dysfunction and secondary tricuspid regurgitation. The presence of 2 left-sided regurgitations may complicate echocardiographic evaluation due to the inapplicability of LV volumetric methods (5,6). Cardiac magnetic resonance imaging may help to quantify regurgitant volumes and ventricular volumes, mass, and function, and hence, may contribute to determine the optimal timing for intervention by assessing the global burden of valve regurgitation (6). Moreover, even when AR and MR are each considered to be moderate in isolation, their combination may result in a severe hemodynamic burden.

In this setting, it is crucial to differentiate primary from secondary MR. These days, primary MR associated with severe AR is mostly degenerative, but may also be due to rheumatic heart disease, drugs, radiation, or infective endocarditis (5). On the other hand, any cause of AR may induce secondary MR as a result of LV remodeling, probably reflecting a longer evolution of the AR and late surgical referral. Secondary MR may also result from concomitant ischemic LV dysfunction, which may further complicate the use of guideline-derived LV diameters and ejection fraction thresholds for surgical management. In 2010, Pai et al. (7) reported that > moderate MR (representing one-quarter of the study population) was independently predictive of reduced survival in a series of 756 patients with severe AR, whereas concomitant mitral valve repair during aortic valve replacement was associated with improved survival. However, the question of whether the survival penalty of significant MR depends on its etiology (i.e., primary or secondary) remained unanswered. Yang et al. (4) report the coexistence of significant MR in 14% of

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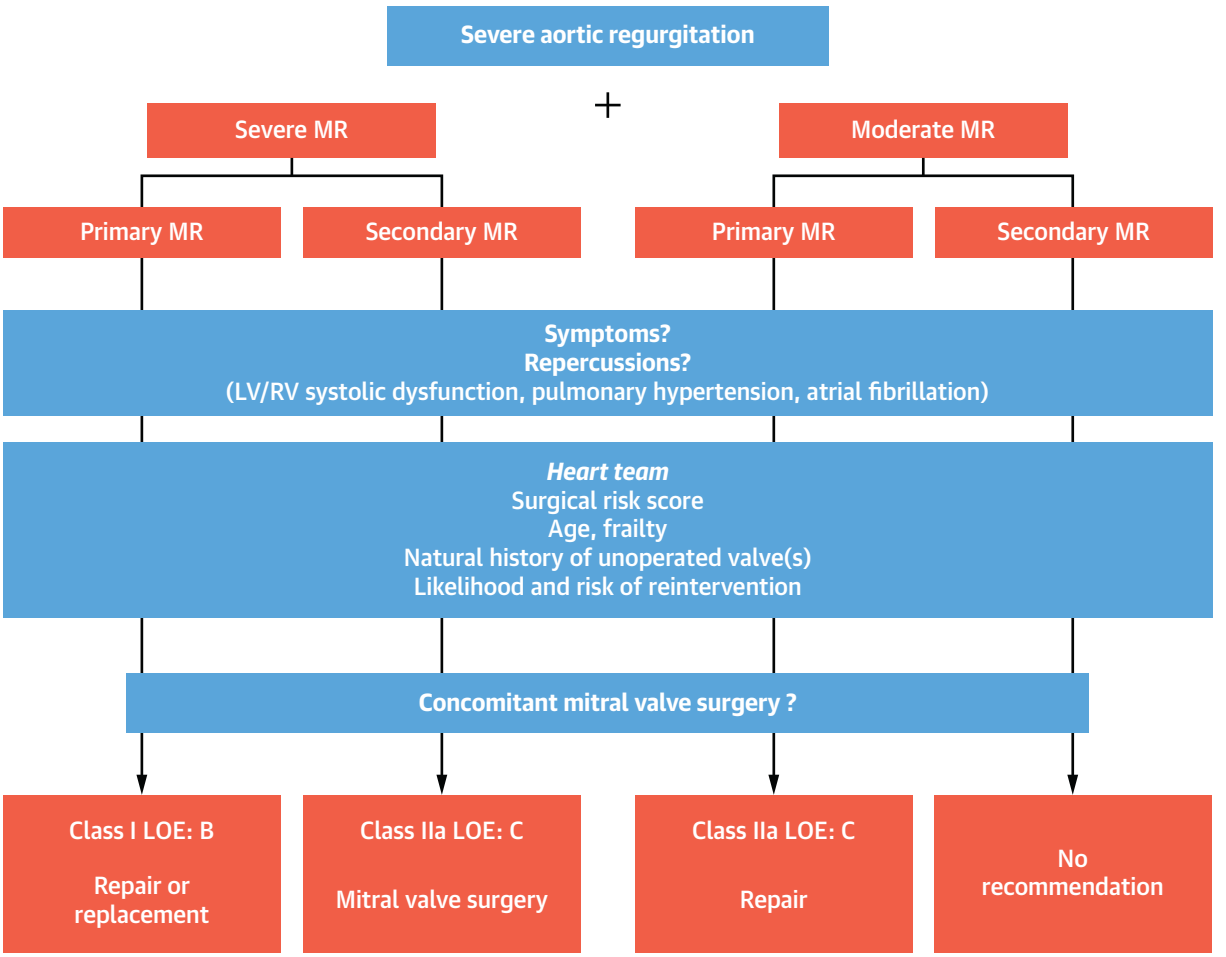
FIGURE 1 **Management Strategy According to the Severity and Etiology of Mitral Regurgitation Based on ACC/AHA Guidelines**



Based on the American College of Cardiology/American Heart Association guidelines (3). LOE = Level of Evidence; LV = left ventricular; MR = mitral regurgitation; RV = right ventricular.

patients in a large retrospective contemporary cohort of 1,239 patients with hemodynamically-significant chronic AR (grades 3 to 4). Functional MR (9%) was more frequent than organic MR (5%) and was primarily due to nonischemic remodeling of the LV. The authors convincingly demonstrate that coexistent MR is associated with excess mortality, with a larger and stronger association with death for secondary than primary MR in age-sex adjusted multivariate comparisons. However, whether the better long-term survival associated with organic MR (relative to functional MR) would have been similar in countries with a higher burden of rheumatic heart disease, and thus in younger patients, is still unclear. Interestingly, the excess mortality risks of pure AR, AR + primary MR, and AR + secondary MR were 1.25-, 1.76-, and 2.34-fold, respectively, relative to the expected survival of an age-matched population. As expected in Western countries, the combination of severe AR with primary MR was mostly degenerative and was associated with advanced age, more symptoms, larger end-systolic diameters, and higher pulmonary pressures than in pure AR. The 8-year rate of surgery was markedly higher in patients with concomitant primary MR than those with isolated AR (91% vs. 55%). Current guidelines provide different LV surgical thresholds for chronic AR (end-systolic diameter 50 mm, ejection fraction 50%) and chronic primary MR (end-systolic diameter 40 to 45 mm, ejection fraction 60%) (2,3), but specific values for the combination of significant AR + MR are lacking. The optimal timing to consider surgery in asymptomatic patients with combined severe AR and significant organic MR is still largely unclear. Indeed, although

the study of Yang et al. (4) is strengthened by its large cohort, the comprehensive echocardiographic data, and its extended duration of follow-up, one cannot ascertain that associated significant MR should prompt physicians to consider surgery in asymptomatic patients. Indeed, the results did not show a survival advantage with surgery (4). However, patients with AR + primary MR experienced poorer survival than those with pure AR, independently of all known surgical triggers (symptoms, LV ejection fraction, and end-systolic diameter index), all of which suggest that associated MR may be an independent incentive for surgery. In this report, secondary MR occurring in patients with severe AR (9% of the cohort) was also associated with worse clinical and echocardiographic features and showed the highest mortality. As nicely highlighted in the discussion section, several observations are consistent with the hypothesis that the development of secondary MR represents an advanced stage within the natural history of AR, including the presence of smaller left-chamber dimensions prior to baseline echocardiography in patients with functional MR, the development of functional MR during follow-up in those with pure AR at baseline, their larger LV and left atrial diameters at baseline echocardiography, and the low proportion of ischemic MR. Interestingly, patients with triple valve disease (AR + MR + tricuspid regurgitation) exhibited the highest risk of death. All of these findings suggest that secondary MR resulting from left chamber remodeling and later functional TR are likely the downstream effects of chronic advanced AR, resulting from longer disease duration and late surgical referral. These results emphasize that AR should not be considered solely as an isolated valvular condition, but rather viewed as a global heart disease, with a continuum of myocardial lesions, as recently proposed for aortic stenosis (8).

Few studies have focused on the effects of aortic valve replacement for AR on the fate of MR. In cases of significant primary MR, an intervention on both valves is generally considered (**Figure 1**). Postoperative LV dysfunction is more likely to occur than in cases of isolated valve regurgitation, but long-term LV function may eventually improve after surgery on both valves (4). On the contrary, if the MR is functional, the common belief is that its severity is likely to spontaneously improve following AR surgery, resulting from reverse LV remodeling and reduced mitral valve deformation (9). However, data are scarce and, to date, the course of secondary MR after isolated aortic valve surgery is largely unpredictable. Nonetheless, surgery on both valves is reasonable in cases of severe secondary MR (**Figure 1**).

The study by Yang et al. (4) provides an important addition to the body of knowledge required to respond to the challenges imposed by MVHD. More data on the natural history and impact of surgery on outcomes, especially in asymptomatic patients, are required to better define the indications, type, and timing of valve interventions. The role of speckle tracking imaging and natriuretic peptides to detect patients most likely to benefit from early intervention should be tested. While waiting for these studies, these patients should be followed in heart valve centers, with a case-by-case management strategy determined by the heart team, considering the severity of each lesion and the risk of the intervention, taking into account the age, comorbidities, and frailty of the patient, as well as the natural history of each valve lesion if left untreated. Undoubtedly, advances in transcatheter valve therapies will change the management paradigm of MVHD in the near future, but definitive data are still lacking.

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