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EDITORIAL COMMENT

# When Aortic Regurgitation Coexists With Aortic Stenosis

## An Extra Burden That Is Difficult to Bear*

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Aortic stenosis (AS) is a common valvular disease (1). An estimated 3.2 million people worldwide have severe AS (1). Severe AS carries a poor prognosis and is associated with a mortality rate of up to 50% within 3-5 years after symptom onset if patients do not undergo valve replacement (1). Aortic valve replacement is indicated to improve symptoms, survival, and left ventricular systolic function (2).

The management of severe aortic stenosis (AS) changed dramatically after 2002 when the first transcatheter aortic valve was implanted in an inoperable patient (3). Refinements in transcatheter aortic valve replacement (TAVR) have expanded management options for patients with severe symptomatic AS, and TAVR is now indicated for patients at high, intermediate, and, most recently, low surgical risk. Surgical aortic valve replacement is currently indicated in selected asymptomatic severe AS patients (4). Despite advances in TAVR therapy, which have expanded management options for severe AS patients, certain populations have not been well studied. One such population is patients with mixed valvular disease. Patients with mixed valvular disease present both diagnostic and therapeutic challenges. The most recent guidelines lack specific recommendations for the surveillance or management of these patients, except that they should be managed in accordance with the predominant valvular lesion guidelines (2,4). There are limited data on the natural history of mixed valvular diseases such as coexisting AS and aortic regurgitation (AR) (2). These patients were historically excluded from major clinical studies. Thus, the optimal timing and choice of intervention remain unclear in this patient population (2).

In this issue of *JACC: Asia*, Ngiam et al (5) examined the natural history of a small number of patients with moderate to severe AS with coexisting AR who did not undergo valve replacement. The authors identified the paucity of literature on the impact of coexisting AR on AS and described clinical and hemodynamic outcomes in this patient population (5). This observational retrospective cohort study identified 1,188 consecutive medically managed patients with moderate to severe AS and preserved left ventricular ejection fraction (LVEF) from a single tertiary center (5). Patients who underwent valve replacement or with polyvalvular disease were excluded (5). A cohort of 88 patients with moderate to severe AR was compared with the remaining 1,100 patients with isolated AS (5). Index clinical and echocardiographic characteristics were compared between the 2 cohorts (5). The 2 groups did not vary significantly in baseline clinical characteristics (5). As expected, patients with coexisting AR had significantly larger left ventricular diastolic diameters, end-diastolic volume indices, stroke volumes, and left ventricular mass and higher mean aortic pressure gradients on their index echocardiograms (5). Patients were followed for at least 3 years to evaluate the incidence of the composite adverse outcome of all-cause mortality or admission for congestive cardiac failure (5). The presence of at least moderate coexisting AR was independently associated with the composite adverse outcome, compared with patients with isolated AS (5). Univariate Cox regression analysis was used to examine

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whether clinical and echocardiographic parameters were associated with the adverse outcome (5). Older age, male sex, ischemic heart disease, smaller aortic valve area, larger left atrial diameters and reduced LVEF were some of the parameters associated with adverse outcomes (5). The presence of coexisting AR remained independently associated with the adverse outcome (hazard ratio [HR]: 1.36) after multivariable Cox regression analysis adjusted for age, aortic valve area, LVEF, and year of echocardiographic study (5). A subgroup cohort of 88 patients with coexisting AR, and 88 patients with isolated AS was created by aortic valve area matching (5). In that matched cohort, coexisting AR remained independently associated with an increased incidence of adverse clinical outcomes (HR: 1.57) (5).

The results of this study are not unexpected, as coexisting significant AS and AR lead to a deleterious effect of combined pressure and volume overload of the left ventricle. The increased afterload generated by the stenotic aortic valve leads to concentric left ventricular hypertrophy, reduced compliance and diastolic dysfunction (2,5,6). The presence of coexisting AR results in added volume overload, which the stiff left ventricle is unable to accommodate. This excess volume contributes to both volume and pressure overload, and patients have increased stroke volumes, higher transaortic peak velocities, and pressure gradients (2,5). Therefore, it is not surprising that coexisting AS and AR have more pathologic consequences than either valvular lesion and portend a worse clinical outcome.

It is important to interpret the study's results in the context of its limitations. These limitations include a relatively small population, the retrospective nature of the study, a lack of matched cohorts, a heterogeneous population, and omission of the symptom status of patients (5). The authors used multivariate Cox regression analysis to control for several confounding variables, but they did not match their initial cohorts and additional confounding variables may have affected their results. The study focused on medically managed patients with significant aortic valve disease, an interesting and overlooked population, given that aortic valve replacement is recommended for many of these patients (2,5). This included patients that were not procedural candidates or who had declined valve replacement (5). By selecting medically managed patients, the study reported on a heterogeneous population that has provided insights into the serious prognosis of patients with mixed aortic valve disease. The presence of symptoms is an important variable that has prognostic and management implications, but unfortunately, this variable was not addressed in the present study. This is a major limitation of the study and affects the generalizability of the study's findings. The authors discuss the index echocardiographic differences between cohorts, which reflect remodeling and hemodynamic changes from the coexisting AR (5). It is not clear how far these patients had progressed in the timeline of their disease at the time of the index study. It would have been helpful to note if patients were symptomatic with these changes, and how these echocardiographic findings would change over time.

Ngiam et al (5) identified a need for defining the natural history and hemodynamic impact of significant AS with coexisting AR. There is currently low-level evidence guiding recommendations for the timing of intervention for mixed AS and AR (4). Current American College of Cardiology/American Heart Association guidelines recommend aortic valve replacement for symptomatic patients with combined AS and AR and transaortic peak velocity of >4.0 m/s or mean transvalvular gradient of 40 mm Hg (Level of Evidence: B), and surgical aortic valve replacement for asymptomatic patients with a peak velocity of >4.0 m/s and LVEF <50% (Level of Evidence: C) (4). Further studies characterizing a timeline of symptom onset, clinical outcomes, and serial echocardiographic changes are crucial to guide the timing of optimal surveillance imaging and interventions in these patients. Patients with AS and coexisting AR may experience more rapid pathologic remodeling, hemodynamic decompensation, and earlier debilitating symptoms as a result of their mixed valvular disease (6). Similar to this study, other studies also have shown that concomitant AR is an independent predictor of adverse events in patients with significant AS (5,7). Coexisting AR carries an increased risk of rapid clinical deterioration, and the onset of symptoms in these patients signifies a more advanced deterioration in myocardial function than in patients with isolated AS (6,7). Mixed aortic valve disease likely needs to be treated earlier than isolated valvular disease, as most patients with asymptomatic moderate mixed aortic valvular disease rapidly develop symptoms and progress to severe disease (6,8). Pursuing an earlier intervention strategy may be favorable in this patient population to prevent irreversible remodeling and long-term consequences

of left ventricular overload. It is also important to consider that asymptomatic patient groups with complex mixed valvular disease and high preoperative surgical risk may become candidates for early interventional management in the future as TAVR continues to rapidly evolve and indications expand. It may be that the added burden of aortic regurgitation signals a more dire prognosis, which should lead to more intense surveillance and earlier valve replacement.

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