

# Outcomes of Asymptomatic Adults with Combined Aortic Stenosis and Regurgitation

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**Background:** The outcomes of patients with mixed aortic valve disease (MAVD; concurrent aortic stenosis [AS] and aortic regurgitation [AR]) and its optimum management are undefined. The aim of this study was to evaluate the natural history of MAVD.

**Methods:** Between 2000 and 2005, 524 asymptomatic adults (mean age,  $66 \pm 14$  years; 306 men) were identified who had mixed AS and AR, who did not undergo early intervention with surgery. The severity of AS and AR was defined using American Society of Echocardiography guideline criteria. Patients were followed over  $5.5 \pm 3.1$  years.

**Results:** Aortic valve replacement (AVR) was performed in 349 patients (67%), and 88 (17%) died. Angina, dyspnea, or syncope developed in 292 patients (84%) before AVR; baseline left ventricular mass and the severity of AS and AR were independent predictors of progression to AVR in the overall group. Survival was associated with younger age (hazard ratio, 1.08;  $P < .001$ ) and valve replacement (hazard ratio, 0.61;  $P = .02$ ). Most patients with MAVD in the moderate category progressed to severe AS or AR by the time of surgery ( $n = 51$  [27%]); symptoms were the main indication in 22 patients. In this group, AVR was associated with age, left ventricular function, valve area, and the change in peak gradient over follow-up. In patients with moderate MAVD, coronary artery disease was present in 38 (20%) at baseline and developed in 21 (21%) during follow-up but was not associated with surgery. The average time to an event (AVR or death) in patients with MAVD was 4 years.

**Conclusions:** Careful surveillance of patients with MAVD is warranted, bearing in mind the composite severity of both AS and AR and their combined hemodynamic effects. (*J Am Soc Echocardiogr* 2014; ■:■-■.)

**Keywords:** Echocardiography, Surgery, Survival, Valves, Aortic stenosis, Aortic regurgitation, Mixed disease

“Mixed aortic valve disease” (MAVD) is a term used to describe concurrent aortic stenosis (AS) and aortic regurgitation (AR). The course and appropriate treatment of MAVD are not well defined. Surgery is indicated in symptomatic patients, as long as operative risks are not unreasonably elevated. However, symptoms (and therefore intervention) might occur in MAVD at a lesser degree of severity than might be expected with either lesion alone. For example, if the AS component causes concentric left ventricular (LV) hypertrophy, the increase in LV end-diastolic volume from significant AR leads the left ventricle to fill on a steeper portion of the pressure-volume curve, potentially causing the earlier onset of symptoms than if concomitant AR were not present. Concomitant AR may also augment LV gradient (through increased stroke volume) and wall tension. These features may explain why the combination of both lesions produces

hemodynamic compromise in patients in whom neither lesion alone seems severe enough to warrant surgery.<sup>1</sup> In asymptomatic MAVD, management is usually determined by the severity of the dominant lesion. The identification of outcome predictors could help with the selection of those patients who could benefit from early valvular surgery.

The purpose of the present study was to evaluate the natural history of MAVD in a large population with extended follow-up, in particular those with mixed moderate disease. Specifically, we sought to determine (1) the risk for and predictors of all-cause mortality in patients who presented with MAVD, (2) predictors of progression to aortic valve replacement (AVR) in unoperated patients, and (3) the rate and major correlates of progression in moderate MAVD.

## METHODS

### Study Patients

From 2000 to 2005, we prospectively used Doppler echocardiography to identify 699 asymptomatic patients  $\geq 18$  years of age with mixed AS and AR without histories of surgery or percutaneous valve intervention. MAVD was defined as the combination of mild or worse AS with mild or worse AR. A subgroup with moderate MAVD was defined by moderate AR or moderate AS, while neither was severe.

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## Abbreviations

AR = Aortic regurgitation

AS = Aortic stenosis

AVR = Aortic valve replacement

CAD = Coronary artery disease

LV = Left ventricular

MAVD = Mixed aortic valve disease

Natural history was defined as the follow-up progression until the end points of mortality or surgery. These patients were followed for procedures, hospital admissions, and mortality in a protocol approved by the institutional review board. Patients ( $n = 130$ ) were excluded if they had surgery within the first 3 months of referral to our center; most of these patients had been followed at outside hospitals before referral to our center

for surgery. After the exclusion of another 23 patients with AR of trivial severity and 22 patients (4%) with inadequate follow-up, the study group comprised the remaining 524 patients (Figure 1).

Clinical symptoms (heart failure, angina, dyspnea, syncope, exercise intolerance, and functional class at the time of presentation) were prospectively recorded at the time of initial echocardiography and recruitment. Previous diagnoses of coronary artery disease (CAD), myocardial infarction, hypertension, smoking, diabetes, hypercholesterolemia, atrial fibrillation, chronic renal failure (serum creatinine  $> 2$  mg/dL), previous surgery or percutaneous coronary intervention, and peripheral vascular disease were documented. Individual variables including systolic blood pressure, diastolic blood pressure, body mass index, glycated hemoglobin, and current medication use including digoxin therapy,  $\beta$ -adrenergic blocker therapy, calcium antagonist therapy, angiotensin-converting enzyme inhibitor therapy, statin therapy, and diuretic drug use were noted (Table 1).

## Echocardiography

Echocardiographic data were obtained using commercially available ultrasound systems. All patients underwent comprehensive examinations, including M-mode and two-dimensional echocardiography and spectral and color Doppler, conducted by an experienced sonographer and interpreted by an echocardiographer using standard criteria. LV size and function were assessed in multiple views, with recordings of chamber and wall dimensions. LV ejection fraction was calculated using the modified Simpson's method.<sup>2</sup>

Valve stenosis was defined as congenital (clear identification of two cusps in systole and systolic cusp doming or highly asymmetric thickening or both), rheumatic (commissural fusion), or degenerative (thickening and increased echogenicity of the cusps with reduced systolic opening). The degree of calcification of the aortic valve was scored as follows: 1 = no calcification, 2 = mildly calcified, 3 = moderately calcified, and 4 = heavily calcified.<sup>3</sup> Continuous-wave Doppler examinations were performed with both imaging and nonimaging transducers, and multiple windows were used to obtain the maximum jet velocity. The maximal instantaneous and mean pressure gradients across the aortic valve were calculated using a modified Bernoulli equation. The aortic valve area was calculated using the continuity equation.<sup>2,3</sup> Mild AS (score 1) is described as aortic valve area  $> 1$  cm<sup>2</sup> and a mean gradient  $\leq 20$  mm Hg. Moderate AS (score 2) is described as aortic valve area  $> 1$  cm<sup>2</sup> and a mean gradient of 20 to 40 mm Hg. Severe AS (score 3) is described as aortic valve area  $< 1$  cm<sup>2</sup>.

The severity of AR was derived using a multiparametric approach.<sup>4,5</sup> Jet size (including vena contracta), descending aortic

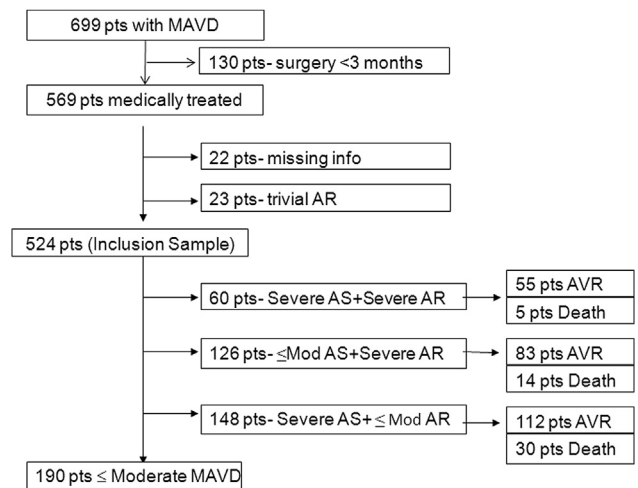


Figure 1 Distribution of patients among categories and their clinical courses.

Table 1 Characteristics of patients with MAVD

Variable	Total group ( $n = 524$ )	Moderate group ( $n = 190$ )
Age (y)	66 $\pm$ 14	65 $\pm$ 14
Men	306 (58%)	111 (58%)
Systolic blood pressure (mm Hg)	133.8 $\pm$ 19.9	133.3 $\pm$ 19.7
Diastolic blood pressure (mm Hg)	71.4 $\pm$ 12.5	72.7 $\pm$ 11.6
Body mass index (kg/m <sup>2</sup> )	27.5 $\pm$ 5.42	28.1 $\pm$ 4.8
Hypertension	253 (48%)	77 (40%)
Diabetes	62 (12%)	23 (12%)
Current/former smokers	176 (34%)	73 (38%)
Hypercholesterolemia	133 (25%)	77 (40%)
Chronic renal failure	16 (3%)	5 (3%)
Atrial fibrillation	75 (14%)	26 (14%)
CAD	96 (18%)	38 (20%)
Peripheral vascular disease	15 (3%)	4 (2%)
Diuretic therapy	165 (31%)	71 (37%)
$\beta$ -blockers	119 (23%)	20 (10%)
Angiotensin-converting enzyme inhibitor therapy	162 (30%)	74 (39%)
Calcium antagonist therapy	76 (14%)	36 (19%)
Digoxin therapy	40 (7%)	20 (10%)
Statin therapy	185 (35%)	77 (40%)
Ejection fraction $< 50\%$	19 (4%)	8 (4%)
Ejection fraction (%)	57.7 $\pm$ 6.3	57.5 $\pm$ 6.6
Aortic valve area (cm <sup>2</sup> )	1.0 $\pm$ 0.3	1.2 $\pm$ 0.2
Aortic mean gradient (mm Hg)	27.7 $\pm$ 14.2	21.5 $\pm$ 10.1

Data are expressed as mean  $\pm$  SD or as number (percentage).

flow reversal, jet density, pressure half-time, and LV function were all used in this process.<sup>1</sup> AR severity was scored as mild (1+), moderate (2+), or severe (3+). The composite severity (ranging from 2 to 6) was created by summing the scale of 1 to 3 for mild, moderate, and severe AS and AR. The association of clinical presentation and echocardiographic features with events, including valve surgery or mortality, was evaluated in a Cox proportional-hazards model in the mixed moderate group.

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