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ORIGINAL INVESTIGATIONS

Outcomes in Moderate Mixed Aortic Valve Disease

Is it Time for a Paradigm Shift?

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ABSTRACT

BACKGROUND A direct comparison of outcomes between moderate mixed aortic valve disease (MAVD) and isolated aortic stenosis (AS) or aortic regurgitation (AR) has not been performed, making evidence-based recommendations difficult in patients with MAVD.

OBJECTIVES This study sought to determine adverse event (AE) occurrence (the primary endpoint), defined as New York Heart Association functional class III/IV symptoms, aortic valve replacement, or cardiac death, and to compare AE rates between MAVD and isolated AS or AR.

METHODS Asymptomatic patients were identified with moderate MAVD and an ejection fraction ≥50% and were followed at Mayo Clinic from 1994 to 2013. Moderate MAVD was defined as a combination of moderate AS and moderate AR. Age- and sex-matched control groups were selected with isolated moderate AR (n = 117), moderate AS (n = 117), or severe AS (n = 117).

RESULTS At 9.1 ± 4.2 years of follow-up, patients with moderate MAVD (n = 251) had a mean age of 63 ± 11 years, 73% were male, and 38% had bicuspid valve. AE occurred in 193 (77%) patients in this group, including symptom development (69%), aortic valve replacement (67%), and cardiac death (4%). Predictors of AE were older age (hazard ratio [HR]: 1.71 per decade; 95% confidence interval [CI]: 1.38 to 1.97 per decade; p = 0.001), and relative wall thickness >0.42 (HR: 2.01; 95% CI: 1.86 to 2.33; p = 0.002). AE rates were similar in the MAVD and severe AS group (71% vs. 68% at 5 years; p = 0.49), but were significantly higher compared with the moderate AS and AR groups.

CONCLUSIONS MAVD patients had outcomes comparable to those with severe AS, and preserved ejection fraction and should be monitored closely for symptoms. (J Am Coll Cardiol 2016;67:2321–9) © 2016 by the American College of Cardiology Foundation.

There is a paucity of data regarding the natural history of combined aortic stenosis (AS) and aortic regurgitation (AR), making evidence-based recommendations regarding aortic valve replacement (AVR) in this subgroup of patients challenging (1–5). In the absence of guideline-directed recommendations for mixed aortic valve disease (MAVD), clinicians often base their decisions on the recommendation for the predominant lesion (2,3,5,6).

For isolated severe AS or AR, AVR is generally recommended in the setting of symptoms, left ventricular (LV) systolic dysfunction, or progressive LV dilation (2,3,5). Conversely, isolated moderate AS or

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ABBREVIATIONS AND ACRONYMS

AE = adverse event

AR = aortic regurgitation

AS = aortic stenosis

AVR = aortic valve replacement

MAVD = mixed aortic valve disease

NYHA = New York Heart Association

moderate AR has a benign prognosis, and as a result, the recommended strategy is conservative management (5,7,8).

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The limited available data on MAVD suggest an aggressive disease course in this population that differs from that of isolated moderate AS or AR (1,4). However, a direct comparison of outcomes between MAVD and isolated AS or AR has not been performed. Our hypothesis was that patients with moderate MAVD had similar outcomes to those with asymptomatic severe AS and preserved ejection fraction and, therefore, should be managed as such.

METHODS

A retrospective study of asymptomatic patients (New York Heart Association [NYHA] functional class I, age ≥18 years) with MAVD followed at Mayo Clinic between January 1994 and December 2013 was performed. MAVD was defined as a combination of moderate AS and moderate AR. MAVD patients were identified from the electronic medical record using free text search software (Advanced Cohort Explorer). Normal LV systolic function (left ventricular ejection fraction [LVEF] ≥50%) and at least 2 years of clinical and echocardiographic follow-up were required for inclusion in the study.

Patients with radiation-induced valvular heart disease, prior endocarditis, prior aortic valve intervention, or coexistent valvular heart disease (defined as moderate or greater stenosis or regurgitation of the mitral, tricuspid, or pulmonary valves) were excluded.

MVAD patients were compared with 3 control groups matched by age (± 5 years) and sex. The first control group comprised patients with isolated moderate AR, the second group patients with isolated moderate AS, and the third group patients with isolated severe AS. Similar to the MAVD cohort, the control groups were asymptomatic and had normal LV function at the beginning of this study.

The control groups were selected from all patients with aortic valve disease followed at Mayo Clinic within the study period. Although there were 251 MAVD patients in the study, only 117 of them had age- and sex-matched control subjects identified in the electronic medical records. To ensure equal numbers of patients in each group, only 117 MAVD patients were included in the comparative analysis.

The primary endpoint was to determine composite adverse event (AE) occurrence, defined as the development of NYHA functional class III or IV symptoms (angina, exertional dyspnea, exertional syncope, or pre-syncope), AVR, or cardiac death (death directly related to cardiac pathology such as congestive heart failure, myocardial infarction, or sudden death). The secondary endpoint was to compare AE rate between the MAVD cohort and the control groups. For AE, only 1 event (the earliest event) was counted per patient. The patients were followed (remained at risk) until the occurrence of primary endpoint, noncardiac death, loss of follow-up defined as no clinic follow-up in 2 years, or at the end of the study period. The Mayo Clinic Institutional Review Board approved this study protocol.

AORTIC VALVE DISEASE SEVERITY CLASSIFICATION. According to published guidelines (2,5,9,10), moderate AS was defined as peak velocity 3.0 to 3.9 m/s and valve area 1.1 to 1.5 cm^2; severe AS as peak velocity ≥4.0 m/s and valve area ≤1.0 cm^2; moderate AR as a combination of at least 2 of the following: vena contracta 0.3 to 0.6 cm, regurgitant volume 30 to 59 ml/beat, effective regurgitant orifice area 0.10 to 0.29 cm^2, and angiographic grade 2+ regurgitation; and severe AR as a combination of at least 2 of the following: vena contracta >0.6 cm, regurgitant volume >60 ml/beat, effective regurgitant orifice area >0.3 cm^2, angiographic grade 3+/4+ regurgitation, and the presence of holodiastolic flow reversal in abdominal aorta.

For this study, the MAVD cohort comprised patients who met both velocity and valve area criteria for moderate AS and at least 2 of the criteria for moderate AR. The moderate AR group comprised patients who met at least 2 of the criteria for moderate AR. The moderate AS group were patients who met both velocity and valve area criteria for moderate AS. The severe AS cohort comprised patients who met both velocity (4.0 to 4.9 m/s) and valve area criteria (≤1.0 cm^2) for severe AS.

DATA COLLECTION. Clinical, echocardiographic, and surgical data were abstracted from medical records. Our definitions for clinical data were the same as used in prior studies (1). The primary and secondary indications for surgery were abstracted from pre-operative clinic notes and from the operation notes.

The LV mass index, relative wall thickness, and LVEF were calculated from M-mode or 2-dimensional echocardiography; the left atrial volume index was calculated by area-length or biplane methods (11,12). Serial echocardiograms were analyzed for each patient in the MAVD cohort to determine the rate of valve disease progression. Diastolic dysfunction was defined as the presence of grade III/IV diastolic dysfunction as documented in the echocardiogram report.

STATISTICAL ANALYSIS. All statistical analysis was performed using JMP version 10.0 software (SAS Institute Inc., Cary, North Carolina). Categorical variables were expressed as percentages, whereas continuous variables were expressed as mean ± SD or median (interquartile range) for skewed data. Comparison of categorical variables was performed using the chi-square test or Fisher exact test, whereas comparison of continuous variables was performed with the 2-sided unpaired Student *t* test or Wilcoxon rank sum test as appropriate. Cox proportional hazard models were used to determine the predictors of AE and are expressed as hazard ratio (HR) and 95% confidence interval (CI).

The AE rates for the MAVD cohort and the control groups were assessed using the Kaplan-Meier method and compared using the log-rank test. The "time-0" or beginning of the "at-risk period" was defined as the time of initial diagnosis of MAVD or isolated valve disease. Only patients who had not reached the primary endpoint, noncardiac death, or loss of follow-up were censored at each time point on the Kaplan-Meier analysis. All p values were 2-sided, and p values <0.05 were considered significant.

RESULTS

We followed 251 patients (mean age 63 ± 11 years; 184 [73%] males) with moderate MAVD for 9.1 ± 4.2 years, including 97 (38%) with bicuspid valve and 39 (16%) with coronary artery disease (Table 1).

In general, we followed patients every 12 to 18 months. Those who developed symptoms were evaluated sooner than their scheduled follow-up. A total of 174 patients (69%) developed NYHA functional class III/IV symptoms during follow-up; 156 of them underwent AVR because of these symptoms, whereas the other 18 did not undergo AVR within the study period. Reasons for foregoing valve replacement in these 18 symptomatic patients were: 6 declined AVR, 4 became symptomatic within the last year of the study and did not undergo valve replacement by study's end, and 8 had unknown reasons.

Over a period of 4.1 ± 2.7 years, 169 patients underwent AVR, of whom 156 (92%) had symptoms. The 13 (8%) patients without symptoms all had severe AS and an abnormal stress test at the time of AVR (Table 1).

VALVE DISEASE PROGRESSION AND OUTCOMES. At the time of AVR, 126 (75%) patients had progressed to severe AS (Table 2). Analysis of serial echocardiograms showed that peak velocity and mean gradient increased by 0.38 ± 0.24 m/s/year and 7 ± 4 mm Hg/year, respectively, whereas aortic valve area decreased by 0.094 ± 0.004 cm^2/year.

TABLE 1 Baseline Characteristics of the MAVD Cohort (n = 251)

Male	184 (73)
Age, yrs	63 ± 11
Follow-up, yrs	9.1 ± 4.2
Echocardiography data	
Aortic peak velocity, m/s	3.5 ± 0.2
Aortic mean gradient, mm Hg	36 ± 2
Aortic valve area, cm^2	1.38 ± 0.06
Aortic valve area index, cm^2/m^2	0.69 ± 0.03
Pressure half time, ms	361 ± 92
LV ejection fraction, %	61 ± 5
LV end-diastolic dimension, mm	53 ± 7
LV end-systolic dimension, mm	33 ± 8
LVMI, g/m^2	139 ± 56
Relative wall thickness	0.41 ± 0.09
LV diastolic dysfunction*	59 (31)
Left atrial volume index, ml/m^2†	31 ± 8
RV systolic pressure, mm Hg	42 ± 5
Aortic dimension, mm	41 ± 6
Clinical data	
Atrial fibrillation	31 (12)
Hypertension	83 (33)
Hyperlipidemia	61 (24)
Coronary artery disease	39 (16)
Bicuspid aortic valve	97 (38)
Rheumatic heart disease	33 (13)
Diabetes	35 (14)
Active smoking	29 (12)
Creatinine clearance <60 ml/min	27 (11)
Body mass index, kg/m^2	28 ± 6
Body surface area, g/m^2	1.6 ± 0.4
Surgical data	
AVR	169 (67)
Bioprosthetic valve	82 (49)
Mechanical valve	87 (51)
CABG	34 (20)
Aorta replacement	28 (17)
Surgical mortality	1 (0.6)

Values are n (%) or mean ± SD. *Diastolic data only available in 189 patients. †Data available in 167 patients. Left atrial volume assessment was performed using area-length and biplane methods.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LV = left ventricular; LVMI = left ventricular mass index; MAVD = mixed aortic valve disease; RV = right ventricular.

At the time of AVR, 24 patients (14%) had progressed to symptomatic severe AR, with LV end-diastolic and -systolic dimensions of 58 ± 6 mm and 42 ± 3 mm, respectively (Table 2).

There were 19 patients (11%) who underwent AVR due to symptom development in the absence of progression to severe aortic valve disease (Table 2). Seventeen of these patients underwent exercise testing, and all 17 patients had abnormal findings including electrocardiographic changes, symptoms (angina and exertional dyspnea), or abnormal blood

TABLE 2 Valve Disease Progression in MAVD Patients Undergoing AVR

	Baseline	At the Time of AVR
Progression of aortic stenosis (n = 126)		
Aortic peak velocity, m/s	3.5 ± 0.2	4.6 ± 0.3
Aortic mean gradient, mm Hg	36 ± 2	49 ± 3
Aortic valve area, cm^2	1.38 ± 0.06	0.88 ± 0.03
LV ejection fraction, %	61 ± 5	57 ± 6
LV end-diastolic dimension, mm	53 ± 7	51 ± 8
LV end-systolic dimension, mm	33 ± 8	33 ± 2
Progression of aortic regurgitation (n = 24)		
Aortic peak velocity, m/s	3.4 ± 0.3	3.9 ± 0.4
Aortic mean gradient, mm Hg	36 ± 3	42 ± 2
Aortic valve area, cm^2	1.41 ± 0.05	1.12 ± 0.06
LV ejection fraction, %	62 ± 7	64 ± 5
LV end-diastolic dimension, mm	55 ± 8	58 ± 6
LV end-systolic dimension, mm	32 ± 6	42 ± 3
No progression of valve disease (n = 19)		
Aortic peak velocity, m/s	3.5 ± 0.3	3.7 ± 0.2
Aortic mean gradient, mm Hg	36 ± 4	38 ± 3
Aortic valve area, cm^2	1.33 ± 0.04	1.27 ± 0.02
LV ejection fraction, %	60 ± 5	63 ± 5
LV end diastolic dimension, mm	53 ± 7	51 ± 8
LV end systolic dimension, mm	33 ± 6	32 ± 7

Values are mean ± SD.
Abbreviations as in Table 1.

TABLE 3 Predictors of Composite Adverse Events in MAVD Patients

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Clinical variables				
Age (per 10-yr difference)	2.63 (2.46–2.89)	<0.0001	1.71 (1.38–1.97)	0.001
Male	1.33 (0.72–2.12)	0.51	2.16 (0.67–4.17)	0.34
Creatinine clearance <60 ml/min	1.23 (0.66–1.76)	0.26		
Smoking	1.37 (0.41–2.16)	0.29		
Atrial fibrillation	1.51 (1.02–2.12)	0.043	2.13 (0.75–2.89)	0.18
Hypertension	2.41 (1.62–3.96)	0.003	3.39 (0.22–8.14)	0.31
Diabetes	1.55 (0.82–2.14)	0.091		
Hyperlipidemia	1.29 (0.68–1.78)	0.25		
Bicuspid aortic valve	1.41 (1.11–1.83)	0.007	1.63 (0.74–2.08)	0.17
Coronary artery disease	2.24 (1.51–3.88)	0.032	1.37 (0.83–2.28)	0.093
Echocardiography variables				
Relative wall thickness >0.42	1.83 (1.26–2.21)	0.003	2.01 (1.86–2.33)	0.002
LVMI (per 10 g/m^2 increase)	1.63 (1.46–2.89)	0.021	1.87 (0.89–2.18)	0.063
LV end-systolic dimension, mm	2.87 (0.31–4.77)	0.19		
LV end-diastolic dimension, mm	1.23 (0.45–1.94)	0.37		
Aortic valve area <0.8 cm^2	2.33 (0.12–6.11)	0.37		
Aortic valve area index <0.5 cm^2	1.83 (0.31–2.79)	0.41		
Mean gradient >35 mm Hg	2.05 (0.61–5.12)	0.41		
Peak velocity >3.5 m/s	1.31 (0.22–4.06)	0.79		
Ejection fraction <55%	1.21 (0.62–1.59)	0.89		
Pressure half time (50 ms decrease)	2.81 (0.44–4.79)	0.22		
Left atrial volume >35 ml/m^2	1.05 (0.61–2.13)	0.46		

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

pressure response during exercise. Assessment of diastolic function was available in 18 patients of whom 14 had grade III/IV diastolic dysfunction. The patients who developed symptoms in the absence of progression of valve disease had more LV hypertrophy compared with the rest of the AVR cohort (relative wall thickness 0.44 ± 0.02 vs. 0.40 ± 0.03; p = 0.038; LV mass index 145 ± 13 g/m^2 vs. 137 ± 44 g/m^2; p = 0.091).

There were 19 deaths (9 cardiac, 8 noncardiac, and 2 unknown) reported during the study period. A total of 10 of these deaths occurred in the AVR arm; 1 occurred perioperatively, with the others due to: congestive heart failure (n = 2), cancer (n = 3), sepsis (n = 1), trauma (n = 1), renal failure (n = 1), and unknown cause (n = 1). A total of 9 deaths occurred in the non-AVR arm and the causes were: congestive heart failure (n = 3), myocardial infarction (n = 2), sudden death (n = 1), stroke (n = 2), and unknown (n = 1).

A total of 193 (77%) patients reached a composite AE endpoint. The multivariable predictors of AE were older age (HR: 1.71 per decade; 95% CI: 1.38 to 1.97 per decade; p = 0.001) and relative wall thickness >0.42 (HR: 2.01; 95% CI: 1.86 to 2.33; p = 0.002) (Table 3).

MAVD COHORT AND CONTROL GROUPS AND OUTCOMES. A total of 117 patients with moderate MAVD were selected and age- and sex-matched to 117 control patients with moderate AS, moderate AR, and severe AS, respectively. Tables 4 and 5 show the baseline characteristics and event occurrence in the MAVD cohort and the control groups.

AVR was performed in 37 (32%) patients in the moderate AR group, 57 (49%) patients in the moderate AS group, and 98 (84%) patients in the severe AS group.

The indication for AVR varied: in the moderate AS group, it was the development of symptomatic severe stenosis (n = 57); in the severe AS group, the indications were symptoms (n = 86) or an abnormal stress test (n = 12); and in the moderate AR group, the indications were the development of symptomatic severe AR plus LV end-systolic dimension >50 mm (n = 33) or LVEF <50% (n = 4).

At the beginning of the study period, the baseline LV end-diastolic and -systolic dimensions for the moderate AR group were 58 ± 6 mm and 36 ± 6 mm, respectively. For the 37 patients that underwent AVR in this group, the LV end-diastolic and -systolic dimensions increased to 68 ± 7 mm and 51 ± 2 mm, respectively, at the time of surgery.

Concomitant aorta replacement was performed in 15 of 93 (16%) MAVD patients who underwent AVR compared with 14 of 98 (14%) patients with severe AS who underwent AVR (p = 0.096). Conversely, the rate of concomitant coronary artery bypass graft (CABG)

TABLE 4 Clinical and Echocardiographic Characteristics of MAVD and Control Groups

	MAVD (n = 117)	Moderate AR (n = 117)	Moderate AS (n = 117)	Severe AS (n = 117)	p Value*
Male	79 (68)	79 (68)	79 (68)	79 (68)	
Age, yrs	64 ± 8	63 ± 8	63 ± 5	64 ± 6	0.853
Follow-up, yrs	8.1 ± 4	7.8 ± 9	9.6 ± 5	7.1 ± 3	0.061
Echocardiography data					
Aortic peak velocity, m/s	3.5 ± 0.2	1.7 ± 0.6	3.4 ± 0.3	4.5 ± 0.4	<0.0001
Aortic mean gradient, mm Hg	36 ± 2	16 ± 7	35 ± 4	48 ± 6	<0.0001
Aortic valve area, cm^2	1.38 ± 0.06	1.81 ± 0.08	1.22 ± 0.07	0.8 ± 0.02	<0.0001
Aortic valve area index, cm^2/m^2	0.69 ± 0.03	0.98 ± 0.04	0.55 ± 0.04	0.41 ± 0.03	<0.0001
Pressure half time, ms	361 ± 92	391 ± 109			
LV ejection fraction, %	61 ± 5	65 ± 7	58 ± 6	56 ± 4	0.19
LV end-diastolic dimension, mm	53 ± 7	58 ± 6	50 ± 6	48 ± 5	0.042
LV end-systolic dimension, mm	33 ± 8	36 ± 6	31 ± 7	28 ± 6	0.051
LV mass index, g/m^2	138 ± 56	94 ± 14	103 ± 31	123 ± 31	0.016
Relative wall thickness	0.40 ± 0.07	0.32 ± 0.04	0.38 ± 0.03	0.42 ± 0.04	0.064
LV diastolic dysfunction	38 (32)	6 (5)	14 (12)	26 (22)	0.024
Left atrial volume index, ml/m^2	31 ± 8	24 ± 5	26 ± 7	29 ± 3	0.17
RV systolic pressure, mm Hg	44 ± 3	33 ± 8	37 ± 8	41 ± 5	0.17
Aortic dimension 46–50 mm	21 (18)	18 (15)	11 (9)	17 (15)	0.096
Aortic dimension >50 mm	3 (3)	0	0	1 (1%)	0.29
Clinical data					
Atrial fibrillation	17 (15)	9 (8)	8 (7)	11 (9)	0.053
Hypertension	34 (29)	35 (30)	39 (33)	41 (35)	0.041
Hyperlipidemia	27 (23)	34 (29)	36 (30)	34 (29)	0.25
Coronary artery disease	18 (15)	14 (12)	17 (15)	21 (18)	0.47
Bicuspid aortic valve	36 (31)	37 (32)	21 (18)	26 (22)	0.037
Rheumatic heart disease	11 (9)	13 (11)	22 (19)	19 (16)	0.082
Diabetes	15 (13)	14 (13)	14 (13)	17 (15)	0.25
Active smoking	11 (9)	11 (9)	13 (11)	9 (8)	0.61
Creatinine clearance <60 ml/min	16 (14)	18 (15)	13 (11)	24 (21)	0.047
Body mass index, kg/m^2	29 ± 4	28 ± 3	31 ± 5	30 ± 4	0.26
Body surface area, g/m^2	1.7 ± 0.2	1.7 ± 0.3	1.9 ± 0.2	1.7 ± 0.3	0.18
Surgical data					
AVR	93 (80)	37 (32)	57 (49)	98 (84)	0.089
AVR with aorta replacement†	15 (16)	4 (10)	5 (9)	14 (14)	0.091
AVR with CABG†	19 (20)	6 (16)	10 (18)	24 (25)	0.014

Values are n (%) or mean ± SD. *Comparison of MAVD and severe aortic stenosis. †Concomitant CABG and aorta replacement calculated as percentage of AVR in each subset.
AR = aortic regurgitation; AS = aortic stenosis; other abbreviations as in Table 1.

surgery was higher in the severe AS group compared with the MAVD group: 24 of 98 (25%) versus 19 of 93 (20%) (p = 0.014) (Table 4).

In the MAVD cohort, the occurrence of NYHA functional class III/IV symptoms was 38% (95% CI: 34% to 42%), 62% (95% CI: 56% to 69%), and 73% (95% CI: 64% to 82%); the occurrence of AVR was 37% (95% CI: 34% to 40%), 65% (95% CI: 57% to 74%), and 76% (95% CI: 69% to 85%); and the occurrence of composite AE was 40% (95% CI: 36% to 44%), 71% (95% CI: 61% to 79%), and 84% (95% CI: 73% to 91%), at 3, 5, and 7 years, respectively.

The composite AE rate in the moderate MAVD cohort was similar to the severe AS group (71% vs. 68% at 5 years; p = 0.49) but was significantly higher than the moderate AS group (71% vs. 31% at 5 years; p < 0.0001) and the moderate AR group (71% vs. 22% at 5 years; p < 0.0001) (Table 5, Central Illustration).

DISCUSSION

The purpose of this study was to determine the outcomes in moderate MAVD and compare these outcomes to matched cohorts with isolated AS or AR. This is the largest study reporting outcomes specifically in patients with moderate MAVD, and it showed that the prevalence of AE was 40%, 71%, and 84% at 3, 5, and 7 years, respectively. The risk factors for AE were older age and increased LV mass, but not the presence of an underlying bicuspid valve.

TABLE 5 Adverse Events in MAVD and Control Groups

	MAVD (n = 117)	Moderate AR (n = 117)	Moderate AS (n = 117)	Severe AS (n = 117)
At last follow-up				
NYHA functional class III/IV symptoms	92 (79)	42 (37)	61 (52)	96 (82)
Aortic valve replacement	93 (80)	37 (32)	57 (49)	98 (84)
Cardiac death	6 (5)	2 (2)	3 (3)	9 (8)
Composite adverse event*	99 (85)	45 (38)	66 (54)	104 (89)
At 5-yr follow-up				
NYHA functional class III/IV symptoms	77 (66)	23 (20)	44 (38)	74 (63)
Aortic valve replacement	69 (59)	19 (16)	39 (33)	74 (63)
Cardiac death	4 (3)	1 (1)	1 (2)	6 (5)
Composite adverse event at 5 yrs	83 (71)	26 (22)	36 (31)	81 (69)

Values are n (%). *Only 1 event was counted for each patient.
NYHA = New York Heart Association; other abbreviations as in Tables 1 and 4.

We also found: 1) AE outcomes in moderate MAVD were comparable to those of isolated severe AS with preserved ejection fraction, but were significantly higher than isolated moderate AS or AR; 2) AS progression was the predominant mechanism for progression of aortic valve disease; and 3) a subset of MAVD patients with concentric hypertrophy tended to become symptomatic requiring AVR even in the absence of any progression in the severity of aortic valve disease.

There are 2 recent studies of outcomes in MAVD (1,4). The first was a prospective study of 71 patients with moderate-to-severe MAVD on the basis of at least moderate AS in combination with at least moderate AR (1). The investigators reported an AE (symptoms, AVR, or cardiac death) rate of 81% at 6 years. Aortic peak velocity was predictive of AE in that series. Apart from a younger patient age (mean age 52 years), the patient demographics and comorbidities were comparable to our cohort. An important difference is that more than two-thirds of that cohort had severe AS or AR at the beginning of the study period.

The second study was a retrospective analysis of 524 patients with MAVD (4), specifically, mild or worse AS plus mild or worse AR. Results showed that 67% of patients required AVR within 4 years and that the risk factors for AE (AVR and death) were older age and increased LV mass at the time of presentation, similar to our findings. One important difference: moderate MAVD comprised less than one-quarter of the study's cohort.

The results of these 2 prior investigations were concordant; both studies suggested that MAVD was associated with higher AE rates compared with historical cohorts of isolated AS or AR. However, the majority of both cohorts already had severe AS or AR at the beginning of the study; as a result, the high event rates reported in these studies were not unexpected.

The outcomes of moderate MAVD are unknown; subsequently, there are no guideline recommendations for the timing of intervention or the frequency of follow-up in this population (2,3,5). A common practice is to extrapolate from guideline recommendations for the predominant lesion (6), which in this case, is either moderate AS or moderate AR. The AE rates for moderate AS have been reported at approximately 25% to 30% at 3 years (13–15), but it is much lower for isolated AR (7,16). Because of the low event rates for moderate AS or moderate AR, the current guidelines recommend conservative management and follow-up every 1 to 2 years to monitor for progression of valve disease in this population (2,5).

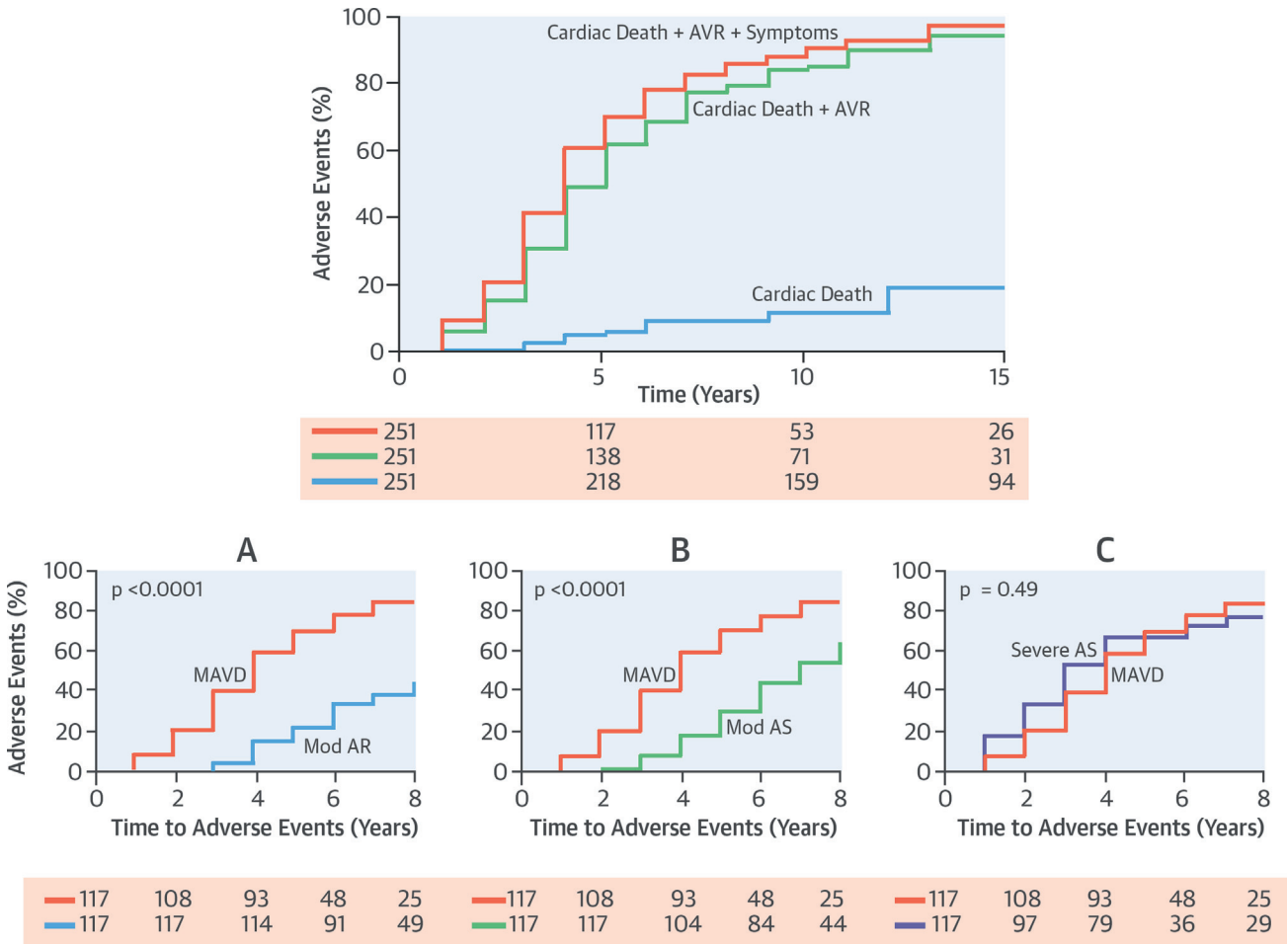
The current study shows an AE rate of 71% at 5 years, which was significantly higher compared with control subjects with moderate AS (31% at 5 years), control subjects with moderate AR (22% at 5 years), or historical cohorts of moderate AS (13–15). An important observation from the current study was that the event rates in those with moderate MAVD were similar to that of a matched cohort with isolated severe AS (peak velocity 4.0 to 4.9 m/s) and historical cohorts of isolated AS (peak velocity 4.0 to 4.9 m/s) (17,18).

PROGRESSION OF AS. The predominant mechanism of progression of valve disease in this study was the progression of stenosis. The aortic peak velocity and mean gradient increased by 0.38 ± 0.24 m/s/year and 7 ± 4 mm Hg/year, respectively, in our cohort. Concordant with the increase in peak velocity and gradient over time, the valve area also decreased, suggesting that the observed increased velocity was not just from increased stroke volume due to worsening AR.

The rate of progression of aortic valve disease has been reported as 0.32 to 0.41 m/s/year in prior series of asymptomatic severe AS (13,17,19) and 0.24 m/s/year in a moderate AS cohort (14). The rate of progression in our cohort was similar to that of severe AS. The annual rate of increase in aortic peak velocity has been shown to be predictive of AE (13,14,19) and may account for the similarity in the occurrence of AE in our cohort compared with isolated severe AS.

PROGRESSION OF AR. Another mechanism for the progression of valve disease in this study was progression of regurgitation. An interesting observation was that none of the 24 (14%) patients who developed symptomatic severe AR achieved an LV end-systolic dimension of 50 mm at the time of AVR, although that is the threshold for recommending AVR for AR (2,5). This also was not observed in 2 prior studies of

CENTRAL ILLUSTRATION **Moderate Mixed Aortic Valve Disease: AE Rates**



Egbe, A.C. et al. J Am Coll Cardiol. 2016;67(20):2321–9.

(Top) Kaplan-Meier curves show adverse event (AE) rates in a cohort of 251 patients with moderate mixed aortic valve disease (MAVD) in terms of cardiac death **(blue)**, aortic valve replacement (AVR) plus cardiac death **(green)**, and the primary endpoint, the composite of New York Heart Association functional class III or IV symptoms, AVR, and cardiac death **(orange)**. **(Bottom)** In the secondary endpoint, 117 patients with MAVD were compared with matched control subjects in terms of composite AE rates. Although event rates were significantly higher for the MAVD cohort compared with **(A)** the isolated moderated aortic regurgitation (Mod AR) group and **(B)** the isolated moderate aortic stenosis (Mod AS) group, rates for the MAVD and severe AS groups were similar **(C)**.

MAVD, even in the subset of patients with symptomatic severe AR (1,4).

We postulate that LV hypertrophy and diastolic dysfunction in MAVD limit the degree of LV dilation in response to the volume load of regurgitation. Also, LV dimensions have not been shown to be predictive of AEs in MAVD (1,4).

SYMPTOM PROGRESSION IN THE ABSENCE OF SEVERE VALVE DISEASE. Another important finding was that 19 (11%) patients developed symptoms requiring AVR, even in the absence of progression of AS or AR. Almost all of these patients had significant diastolic dysfunction and concentric LV hypertrophy.

The combined effect of pressure-related LV hypertrophy due to AS and volume overload due to AR decreases the operative compliance of the LV resulting in a greater rise in diastolic pressure per unit of volume increase in the LV during the diastolic filling period (20). We speculate that the occurrence of symptoms in this subset of patients in the absence of severe aortic valve disease was due to diastolic dysfunction caused by the deleterious effect of combined pressure and volume load on the LV. In support

of our speculation, Honda et al. (21) showed that concomitant AR in the setting of AS was predictive of symptoms, hospitalization, and all-cause mortality.

STUDY LIMITATIONS. First, the retrospective nature of this study, using a cohort from a single tertiary center, may have resulted in some selection bias. Second, some of the patients underwent CABG and aorta replacement at the time of AVR, making it difficult to accurately determine the primary indication for surgery in these cases. Because the proportion of patients who underwent concomitant CABG and aorta replacement was similar in the MAVD and severe AS subgroups, we believe that the confounding effect of this limitation is eliminated or at least significantly minimized.

Also, some of the patients did not undergo exercise testing prior to surgery; moreover, even in those with an abnormal stress test, our results are not analyzed on the basis of the results of exercise testing because of the differences in exercise test modalities used in the study. Only the patients who met both velocity and valve area criteria for severe AS were included in the severe AS cohort. As a result, we excluded patients with AS who had discordant velocity and valve areas results. A blinded critical endpoint committee did not review the endpoints. Lastly, our mortality data may be underestimated because we relied on mortality data as reported to the clinic. However, any bias introduced by underestimation of mortality in MAVD patients will be balanced by similar underestimation in the control groups.

CONCLUSIONS

The AE outcomes in moderate MAVD appeared to be similar to those with asymptomatic isolated severe AS with preserved LV systolic function. This suggests that it would be inappropriate to apply guideline recommendations for isolated moderate AS or moderate AR to this population. Additionally, a subset of moderate MAVD patients with concentric hypertrophy can become symptomatic even in the absence of severe aortic valve disease.

On the basis of these findings, we recommend that patients with moderate MAVD be followed every 6 to 12 months and monitored closely for rapid progression of valve disease or development of symptoms, similar to patients with isolated severe AS. Early valve replacement may be considered for MAVD patients without comorbidities in centers with low risk for such procedures.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with mixed AS and AR of moderate severity experience AE rates comparable to those with asymptomatic severe AS who have a preserved LVEF. Concentric LV hypertrophy is associated with the onset of symptoms even without progression of valve disease.

TRANSLATIONAL OUTLOOK: Prospective studies with long-term follow-up are needed to determine the optimum timing of valve replacement in patients with moderate MAVD.

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