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ORIGINAL RESEARCH

The Mitral Annular Disjunction of Mitral Valve Prolapse

Presentation and Outcome

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ABSTRACT

OBJECTIVES The aim of this study was to assess in patients with mitral valve prolapse (MVP) mitral annular disjunction (MAD) prevalence, phenotypic characteristics, and long-term outcomes (clinical arrhythmic events and excess mortality).

BACKGROUND Clinical knowledge regarding MAD of MVP remains limited and controversial, and its potential link with untoward outcomes is unsubstantiated.

METHODS A cohort of 595 (278 women, mean age 61 ± 16 years) consecutive patients with isolated MVP, with comprehensive clinical, rhythmic, Doppler echocardiographic, and consistent MAD assessment, were examined. MAD prevalence, associated MVP phenotypes, and outcomes (survival, clinical arrhythmic events) starting at diagnostic echocardiography were analyzed. To balance important baseline differences, propensity scoring matching was conducted among patients with and those without MAD.

RESULTS The presence of MAD was common (n = 186 [31%]) in patients with MVP, generally in younger patients, and was not random but was independently associated with severe myxomatous disease involving bileaflet MVP and marked leaflet redundancy (both $P \leq 0.0002$). The presence of MAD was also independently associated with a larger left ventricle ($P = 0.005$). Age-matched cohort survival after MVP diagnosis was not worse with MAD (10-year survival 93% ± 2% for patients without MAD and 97% ± 1% for those with MAD; $P = 0.40$), even adjusted comprehensively for MVP characteristics ($P = 0.80$) and accounting for time-dependent mitral surgery ($P = 0.60$). During follow-up, 170 patients had clinical arrhythmic events (ventricular tachycardia, n = 159; arrhythmia ablation, n = 14; cardioverter-defibrillator implantation, n = 14; sudden cardiac death, n = 3). MAD was independently associated with higher risk for arrhythmic events (adjusted HR: 2.60; 95% CI: 1.87-3.62; $P < 0.0001$). The link between MAD and arrhythmic events persisted with time-dependent mitral surgery (adjusted HR: 2.54; 95% CI: 1.84-3.50; $P < 0.0001$), was strong under medical management (adjusted HR: 3.21; 95% CI: 2.03-5.06; $P < 0.0001$) but was weaker after mitral surgery (adjusted HR: 2.07; 95% CI: 1.24-3.43; $P = 0.005$).

CONCLUSIONS This large cohort with MVP comprehensively characterized shows that MAD is frequent at MVP diagnosis and is strongly linked to advanced myxomatous degeneration. The presence of MAD was independently associated with long-term excess incidence of clinical arrhythmic events. However, within the first 10 years post-diagnosis, MAD was not linked to excess mortality, and although reassurance should be provided from the survival point of view, careful monitoring for arrhythmias is in order for MAD. (J Am Coll Cardiol Img 2021;14:2073-2087) © 2021 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

ICD = implantable cardioverter-defibrillator

LV = left ventricle

LVEF = left ventricular ejection fraction

MAD = mitral annular disjunction

MR = mitral regurgitation

MVP = mitral valve prolapse

PVC = premature ventricular contraction

VF = ventricular fibrillation

VT = ventricular tachycardia

Mitral valve prolapse (MVP), affecting 2.4% of the population (1), is the most frequent cause of organic mitral regurgitation (MR) in Western countries (2). The mitral annulus to which leaflets are attached is the reference regarding MVP diagnosis, for which criteria were revised to account for annular saddle shape (3,4). With these diagnostic criteria ascertained, population and cohort studies have demonstrated that outcome is related mainly to MR severity and consequences (5–7). However, the importance of the mitral annulus was also emphasized in early autopsy studies (8,9) describing anomalous attachment of the posterior leaflet, directly on the atrial wall, known as mitral annular disjunction (MAD). Such particularity is characterized by disinsertion of the normal mitral annular structure, comprising the atrial-valvular-ventricular junction, with remaining posterior leaflet attachment on the atrial wall (atrial-valvular junction) (4). With careful high-resolution imaging, MAD is now reliably visualized on transthoracic (10,11) and transesophageal (12) echocardiography or cardiac magnetic resonance (13,14). Although surgical series emphasize potential MAD correction by suture annuloplasty (12), clinical information regarding MAD is quite limited and controversial.

Indeed, the prevalence of MAD in patients with MVP is reported with considerable variation in small series including various MR severity grades (11,12,15,16) or confined to severe MR (17). Associated phenotypic MVP characteristics remain profoundly uncertain, probably because of small sample sizes examined, and MAD has been alternatively theorized as preceding MVP occurrence (8), as independent of MVP (13,15), or as a by product of myxomatous MVP (11,12). However, most importantly, and in the absence of large cohorts (18) assessing MAD at MVP diagnosis with long-term follow-up, the outcome of MAD remains uncertain. Widely contrasting reports suggest a benign nature (16) with rare MVP complications (15), whereas in stark contrast, other reports have linked MAD to serious ventricular arrhythmias (19,20), with some case reports (9), and reviews (21,22) emphasizing MAD as a harbinger and "red flag" for sudden death.

To fill these gaps in knowledge, a large cohort of patients with isolated MVP, with comprehensive Doppler echocardiographic characterization of MAD and mitral leaflet characteristics, detailed rhythmic assessment by Holter monitoring, and long-term outcome monitoring starting at diagnostic echocardiography, is required. We gathered such a unique cohort, defining MAD at MVP diagnosis, and aimed to describe the prevalence of MAD, to identify potential MVP phenotypes associated with MAD, and to uncover potential associations with subsequent severe clinical arrhythmic events and excess mortality after MVP diagnosis.

METHODS

Eligibility was screened in all consecutive patients with 1) aged ≥18 years; 2) isolated MVP, with or without flail leaflet, first diagnosed at the Mayo Clinic in Rochester, Minnesota, from 2003 to 2011; 3) comprehensive clinical and echocardiographic evaluation at diagnosis, including symptoms, clinical history, and comorbidities; 4) arrhythmia evaluation by 24-h Holter monitoring during follow-up; and 5) available electronic echocardiographic images for detailed morphologic assessment. Subjects were excluded if they denied research authorization (per Minnesota law) or presented with: 1) moderate or greater aortic regurgitation or stenosis; 2) moderate or greater mitral stenosis; 3) previous valvular surgery; 4) congenital heart disease (patent foramen ovale was not excluded); 5) hypertrophic, infiltrative, restrictive cardiomyopathy or pericardial constriction; and 6) arrhythmic cardiomyopathy including arrhythmogenic/right ventricular cardiomyopathy, arrhythmogenic dilated cardiomyopathy, lamin A/C cardiomyopathy, or long-QT syndrome. As this was a low-risk study, the requirement to obtain written informed consent was waived by the Mayo Clinic institutional Review Board, which approved this study.

ECHOCARDIOGRAPHIC EVALUATION. Comprehensive Doppler echocardiographic examination under direct supervision of a Mayo consultant in routine practice followed standard imaging protocol and guidelines (23). Degenerative MR integrative grading used specific, supportive, and quantitative (if possible) measures to classify degenerative MR as absent to severe according to American Society of Echocardiography recommendations. All standard measurements performed at diagnosis were downloaded from the digital echocardiographic repository without alteration. Nonstandard measurements of mitral leaflet length and thickness, leaflet redundancy presence and severity, and MAD presence and maximum length were performed on digitally stored images without knowledge of outcome and arrhythmia characteristics. Leaflet length and thickness were measured during diastole in the parasternal long-axis view. Leaflet redundancy was

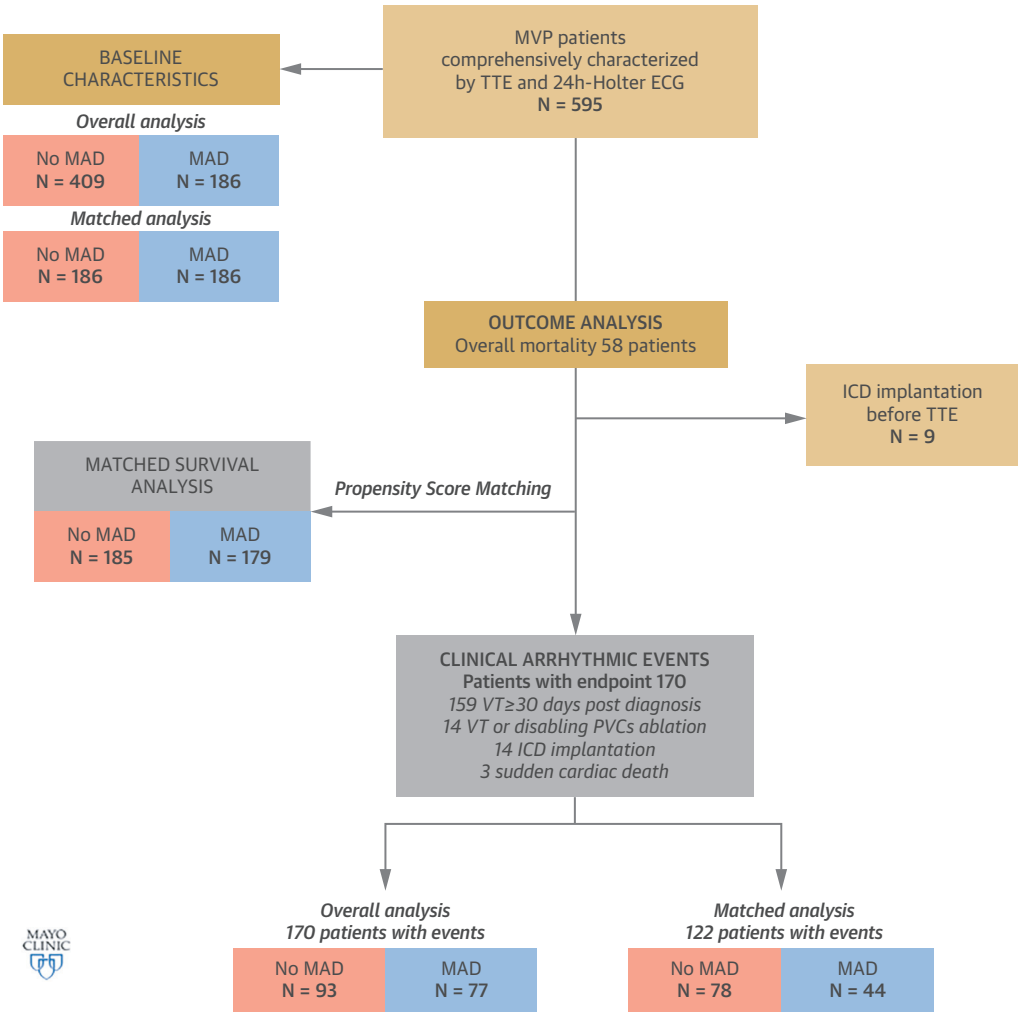
TABLE 1 Baseline Characteristics

	Overall Population (N = 595)	No MAD (n = 409)	MAD (n = 186)	*P* Value
Clinical characteristics				
Age, yrs	61 ± 16	63 ± 16	57 ± 15	<0.0001
Female	278 (47)	184 (45)	94 (51)	0.20
BMI, kg/m^2	25 ± 5	26 ± 5	24 ± 4	0.003
Heart rate, beats/min	68 ± 14	69 ± 15	67 ± 12	0.10
Atrial fibrillation	107 (18)	90 (22)	17 (9)	<0.0001
Hypertension	227 (38)	175 (43)	52 (28)	0.0005
Diabetes	43 (7)	31 (8)	12 (6)	0.60
Dyslipidemia	242 (41)	176 (43)	66 (35)	0.08
History of CAD	135 (23)	113 (28)	22 (12)	<0.0001
History of congestive heart failure	46 (8)	38 (9)	8 (4)	0.03
Charlson index	0.84 ± 1.10	0.96 ± 1.19	0.58 ± 0.78	<0.0001
Symptoms				
History of syncope	66 (11)	38 (9)	28 (15)	0.04
Chest pain	110 (18)	83 (20)	27 (15)	0.09
Palpitation	213 (36)	135 (33)	78 (42)	0.04
Dyspnea	210 (35)	153 (37)	57 (31)	0.10
Edema	53 (9)	47 (11)	6 (3)	0.0004
Echocardiographic variables				
Bileaflet	280 (47)	141 (34)	139 (75)	<0.0001
Posterior	232 (39)	189 (46)	43 (23)	<0.0001
Flail leaflet	60 (10)	48 (12)	12 (6)	0.04
Mitral leaflets length, mm				
Anterior	23 ± 4	22 ± 4	24 ± 5	<0.0001
Posterior	15 ± 4	15 ± 4	16 ± 4	0.0002
Mitral leaflet proximal thickness, mm				
Anterior	2 ± 1	2 ± 1	3 ± 1	0.0009
Posterior	2 ± 1	2 ± 1	3 ± 1	<0.0001
Mitral leaflet redundancy	283 (48)	159 (39)	124 (67)	<0.0001
LVEDD, mm	52 ± 7	51 ± 6	54 ± 7	<0.0001
Indexed LVEDD, mm/m^2	28 ± 4	27 ± 3	29 ± 4	<0.0001
LVESD, mm	33 ± 6	33 ± 6	34 ± 6	0.01
Indexed LVESD, mm/m^2	18 ± 3	17 ± 3	18 ± 3	0.001
LVEF, %	62 ± 7	62 ± 7	63 ± 7	0.50
LAVI, mL/m^2	44 ± 21	44 ± 22	45 ± 22	0.60
Mitral regurgitation				0.04
None/trivial	215 (36)	160 (39)	55 (30)	
Mild	47 (8)	32 (8)	15 (8)	
Moderate	167 (28)	101 (25)	66 (35)	
Severe	166 (28)	116 (28)	50 (27)	
ERO, mm^2	15 (0-29)	13 (0-29)	18 (0-31)	0.20
RVol, mL	25 (0-50)	23 (0-52)	29 (0-46)	0.60
Medications				
ARBs	59 (10)	47 (11)	12 (6)	0.05
ACE inhibitors	175 (29)	132 (32)	43 (23)	0.02
Anti-HTN medications	410 (69)	295 (72)	115 (62)	0.01
Statins	187 (31)	147 (36)	40 (22)	0.0003
Aspirin	368 (62)	265 (65)	103 (55)	0.03
Digoxin	51 (9)	41 (10)	10 (5)	0.05
Antiarrhythmic agents	110 (18)	85 (21)	25 (13)	0.03
Calcium inhibitors	108 (18)	92 (22)	16 (9)	<0.0001
Beta-blockers	310 (52)	221 (54)	89 (48)	0.20
Diuretic agents	183 (31)	143 (35)	40 (22)	0.008

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; ERO = effective regurgitant orifice; HTN = hypertension; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MAD = mitral annular disjunction; MR = mitral regurgitation; RVol = regurgitant volume.

FIGURE 1 Study Population Flowchart for Baseline Characteristics and Outcome Analysis

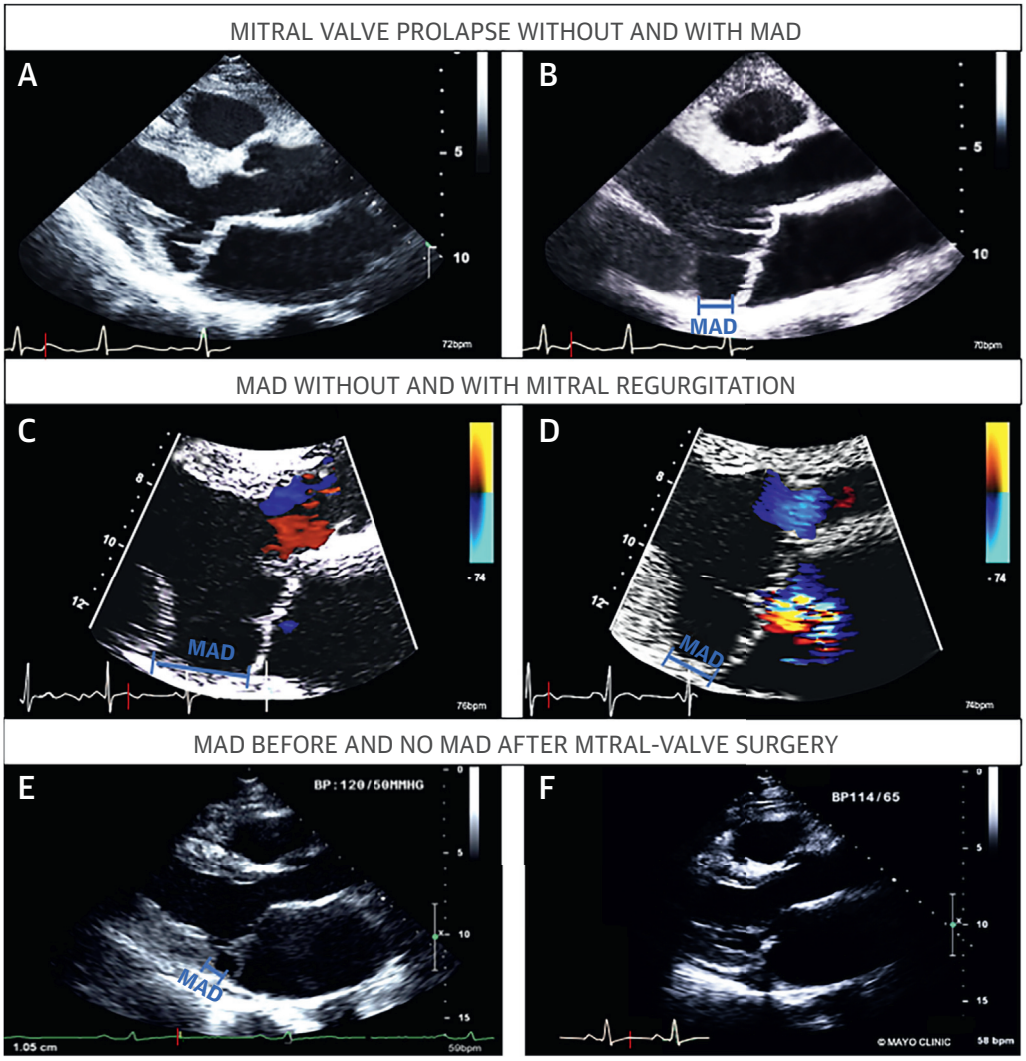


The total number of patients with isolated mitral valve prolapse (MVP) and 24-h Holter electrocardiography diagnosed between 2003 and 2011 is represented in the **upper box**. For baseline characteristics, patients were stratified by presence or absence of mitral annular disjunction (MAD) in overall and matched 1:1 cohorts. For outcome analysis, patients with implantable cardioverter-defibrillators (ICDs) before transthoracic echocardiography (TTE) were excluded. Clinical and arrhythmic events were then recorded in both overall and age-matched cohorts and presented stratified by MAD. PVC = premature ventricular contraction; VT = ventricular tachycardia.

graded by evaluating mitral excess tissue, while thickening was graded semiquantitatively. MAD distance was measured in the parasternal long-axis view at end-systole as the distance between the mitral annulus and the systolic bulge of the ventricular myocardium (8,9).

ELECTROCARDIOGRAPHIC CHARACTERIZATION. Holter recordings reviewed by an electrophysiologist blinded to clinical, echocardiographic, and outcome data involved full tracings, heart rhythm, heart rate, and presence and burden of premature ventricular contractions (PVCs) over 24 h. Number, average beats, rate, and duration of ventricular tachycardia (VT) events were noted. Ventricular arrhythmia diagnosis referred to the standard state-of-the-art approach of 3-lead electrocardiography (24), with VT graded as previously recommended (25-27), as VT runs ≥3 beats with a rate ≥120 beats/min. Ventricular runs <120 beats/min were not considered VT (28). Ventricular arrhythmia (VT or disabling PVCs) ablation and implantable cardioverter-defibrillator (ICD) requirement for ventricular arrhythmic events were recorded.

FIGURE 2 **MVP and MAD**



Transthoracic echocardiographic long-axis view in end-systole displaying MVP with **(A)** absence of MAD and **(B)** MAD; MVP and MAD with **(C)** no mitral regurgitation (MR) and **(D)** severe MR; **(E)** MVP and MAD of 11-mm length before surgery and **(F)** absence of MAD after mitral valve repair. BP = blood pressure; other abbreviations as in Figure 1.

DEMOGRAPHIC AND CLINICAL DATA. Demographic and clinical data were extracted electronically from the patient's medical record, including vital signs and comorbidities (summated using the Charlson index). History of previous VT or ventricular fibrillation (VF) with ICD was retrieved. Symptoms were collected from clinical notes using natural-language processing.

FOLLOW UP. The main outcome measure was overall survival throughout follow-up in unmatched and matched cohorts. The secondary endpoint, a composite of clinically significant arrhythmias, including VT occurrence, VT or disabling PVC ablation, ICD implantation, and sudden cardiac death during follow-up, was gathered using Holter monitoring, Mayo electronic repositories of electrophysiological ablations and defibrillator implantations, and clinical notes on outside interventions. Death occurrence and date were extracted using Accurint, a comprehensive proprietary resource of vital status provided by LexisNexis, gathering multiple national sources, including the Social Security Death Index (not limited to Minnesota), interrogated in mid-2019. To ensure accurate mortality counts, patients considered alive

TABLE 2 MAD Phenotype

Determinants of MAD Phenotype	Univariate Analysis		Multivariate Analysis[a]	
	OR (95% CI) for Ventricular Ectopy Presence	*P* Value	OR (95% CI) for Ventricular Ectopy Presence	*P* Value
Age (per 10 y)	0.80 (0.72-0.89)	<0.0001	0.98 (0.97-0.99)	0.002
Female	1.25 (0.55-1.13)	0.20	1.65 (1.03-2.54)	0.04
LVEF (per 10%)	1.54 (0.37-6.40)	0.60	1.79 (1.11-2.87)	0.01
LVESD (per 10 mm)	4.63 (1.35-15.93)	0.02	2.41 (1.30-4.49)	0.005
Redundant leaflets	3.17 (2.20-4.58)	<0.0001	2.90 (1.91-4.22)	<0.0001
Bileaflet MVP	5.62 (3.81-8.29)	<0.0001	5.18 (3.37-7.99)	<0.0001
Flail leaflet	0.52 (0.27-1.00)	0.04	0.88 (0.37-2.08)	0.80
Moderate or greater MR	0.93 (0.63-1.37)	0.70	0.62 (0.34-1.11)	0.10

[a]Adjusted for age, sex, LVEF, LVESD, redundant leaflets, bileaflet MVP, flail leaflet, and MR severity.
MVP = mitral valve prolapse; OR = odds ratio; other abbreviations as in Table 1.

by Accurint were censored on December 31, 2018. Because of legal restrictions, ascertainment of all causes of death on death certificates was not possible, and overall survival was the main measure of mortality.

STATISTICAL ANALYSIS. Results are expressed as mean ± SD, median (interquartile range), or percentages, and differences between MAD and absence of MAD were compared using standard chi-square tests without Fisher adjustment, analysis of variance, or the Wilcoxon test. Characteristics associated with MAD were assessed using univariable and multivariable logistic regression. Because mitral leaflet length and thickness (as continuous and categorical) and leaflet redundancy were highly associated ($P < 0.0001$ for all), only leaflet redundancy grading was included in multivariable models. Odds ratios for MAD presence (vs absence) were reported unadjusted and in multivariable analysis. Fitting of models was summarized using C statistics.

Survival and freedom from arrhythmic events (VT, ventricular arrhythmia ablation, ICD implantation, and sudden cardiac death) were displayed using the Kaplan-Meier method and compared using the log-rank test. Follow-up VT was considered >30 days after MVP diagnosis to focus on long-term outcomes. Ventricular arrhythmia or severe PVC ablations, ICD implantations, and sudden cardiac death were recorded any time after index echocardiography. Holter timing was stratified under medical management versus after mitral surgery. For both endpoints, patients with VT or VF arrhythmia history leading to previous ICD implantation for arrhythmic death prevention were excluded from the analysis. Cox proportional hazards regression models analyzing the association of MAD with outcome were adjusted for age, sex, comorbidity index, symptoms, atrial fibrillation, left ventricular ejection fraction (LVEF), and MR grade incrementally. Because of the age difference between groups, patients with MAD were matched to control subjects without MAD using a greedy nearest neighbor propensity score matching algorithm. Success of propensity matching was assessed by comparing distributions in matched subsets (an absolute standardized difference <10% indicated a small imbalance), followed by Cox proportional hazards adjustment for persistent differences. Linking VT to subsequent mortality (irrespective of MAD presence) was also analyzed from arrhythmia evaluation as index time (ie, at Holter performance). HRs associated with MAD are presented with 95% CIs. A time-dependent term for mitral surgery assessed whether it affected the link between MAD and outcome. The *P* values <0.05 were considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. All consecutively eligible patients diagnosed with isolated MVP were included in the cohort, which encompassed 595 patients (278 women, mean age 61 ± 16 years). Baseline demographic and clinical characteristics, presented in Table 1, are typical for a wide-ranging MVP cohort. Bileaflet MVP was found in 280 patients (47%), flail leaflet in 60 (10%), and marked leaflet redundancy in 283 (48%), with the anterior leaflet measuring 23 ± 4 mm and the posterior leaflet 15 ± 4 mm. MR was absent or trivial in 36%, mild in 8%, and moderate in 28%, while 28% had severe MR (median effective regurgitant orifice area 15 mm^2; interquartile range: 0-29 mm^2). Clinically, 23% of patients had histories of coronary artery disease (CAD), 38% had hypertension, 18% had atrial fibrillation, and 11% had histories of syncope, with a low comorbidity index of 0.84 ± 1.10.

TABLE 3 Association of MAD With Outcome in Overall Cohort

		Mortality		Any Severe Ventricular Arrhythmic Event	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Univariable	MAD[a]	0.30 (0.14-0.65)	0.003	Overall	
				2.16 (1.59-2.92)	<0.0001
				Arrhythmia under medical management	
				2.56 (1.71-3.82)	<0.0001
				Arrhythmia after mitral surgery	
				1.57 (0.99-2.49)	0.05
Adjusted for age, sex, and Charlson index	MAD[a]	0.55 (0.25-1.24)	0.10	Overall	
				2.45 (1.78-3.36)	<0.0001
				Arrhythmia under medical management	
				2.89 (1.89-4.40)	<0.0001
				Arrhythmia after mitral surgery	
				1.81 (1.17-2.95)	0.02
Further adjustment for symptoms, AF, LVEF, and MR grade	MAD[a]	0.62 (0.27-1.41)	0.30	Overall	
				2.60 (1.87-3.62)	<0.0001
				Arrhythmia under medical management	
				3.21 (2.03-5.06)	<0.0001
				Arrhythmia after mitral surgery	
				2.07 (1.24-3.43)	0.005

[a]Compared with no MAD.

AF = atrial fibrillation; other abbreviations as in Tables 1 and 2.

Overall, left ventricular (LV) dilatation was mild, mean LVEF was 62% ± 7%, and mean left atrial volume index was 44 ± 21 mL/m^2. MAD was diagnosed in 186 patients (31%), measuring 7.5 ± 2.8 mm. History of previous aborted sudden cardiac death caused by proven VT or VF indicating ICD was found in 9 patients (of whom 7 were diagnosed with MAD) (Figure 1).

Table 1 shows baseline characteristics compared between patients without MAD (Figure 2A) and those with MAD (Figure 2B). Patients with MAD had younger age, lower Charlson index, and less history of CAD, heart failure, hypertension, and atrial fibrillation ($P \leq$ 0.04 for all). Patients with MAD had more symptoms of syncope or palpitation compared with those without MAD, but there were no differences in sex and proarrhythmic or beta-blocker medications.

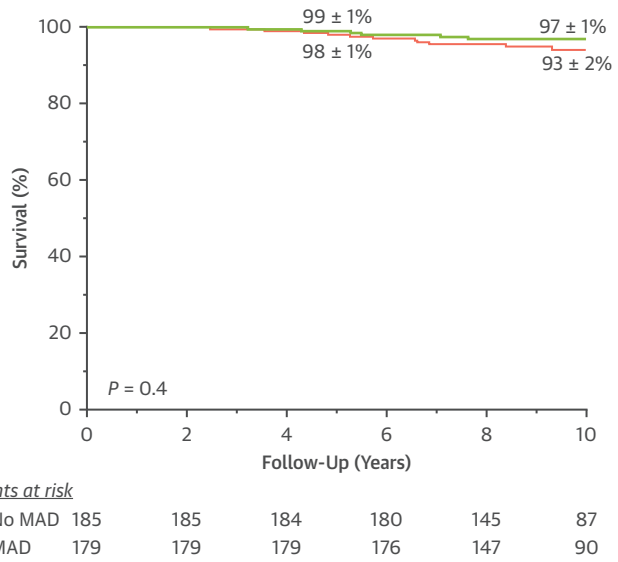
Morphologically, MAD was associated with bileaflet prolapse and longer and more redundant leaflets. Also, patients with MAD had larger left ventricles, with no differences in left atrial volume index and LVEF and comparable MR severity by integrative grading (vs patients without MAD) (Figures 2C and 2D).

Characteristics of matched subsets of patients with and those without MAD (n = 372) (Figure 1) show (Supplemental Table 1) excellent balance for age, body mass index, atrial fibrillation, history of CAD, comorbidity index, and LVEF ($P \geq$ 0.20). Similar to the main cohort, matched patients with MAD (vs those without MAD) presented with predominantly severe myxomatous disease, frequent bileaflet MVP, and longer and redundant leaflets. Although MAD in age-matched patients remained associated with a larger left ventricle, a slight trend pointed to more MR and a larger left atrium.

Stratifying patients with MAD by ventricular arrhythmia, those with ventricular arrhythmia were older with more redundant or longer leaflets, longer MAD, and larger left ventricles ($P \leq$ 0.04) (Supplemental Table 2).

CHARACTERISTICS ASSOCIATED WITH MAD PHENOTYPE. Clinical and echocardiographic characteristics associated with MAD are presented in Table 2. Univariably, younger age and larger left ventricular end-systolic diameter were associated with MAD and persisted in multivariable analysis ($P \leq$ 0.005 for both). Morphologically, absence of flail leaflet was univariately associated with MAD but not in multivariable analysis. Conversely, 2 morphologic characteristics were strongly and independently associated with MAD: marked leaflet redundancy (Table 2), with a univariate odds ratio of 3.17 (95% CI: 2.20-4.58; $P <$ 0.0001), almost unchanged after

FIGURE 3 Survival of Matched Cohort Stratified by Presence of MAD



Survival stratified by mitral annular disjunction (MAD) groups matched for age, body mass index, coronary artery disease history, atrial fibrillation, and comorbidity index. Note the comparable mortality between MAD groups. Values are estimated survival ± SE.

adjustment (2.90; 95% CI: 1.91-4.22; $P < 0.0001$), and bileaflet MVP, with an odds ratio of 5.62 (95% CI: 3.81-8.29; $P < 0.0001$) univariably, remaining high (5.18; 95% CI: 3.37-7.99; $P < 0.0001$) post-adjustment (model C statistic = 0.79).

Female sex and higher LVEF, not associated with MAD univariably, contributed modestly to the model post-adjustment. Conversely, no independent link between MAD and MR severity was observed ($P = 0.10$) (**Table 2**).

Modeling of MAD-associated characteristics within matched subsets (Supplemental Table 3) confirmed strong associations of MAD with marked leaflet redundancy, bileaflet prolapse, and LV enlargement ($P \leq 0.02$). In multivariable analysis, no other characteristic was associated with MAD, confirming the lack of association of MR severity with MAD ($P \geq 0.10$).

Echocardiographic MAD phenotype (vs absence of MAD), stratified by MR severity, showed enlarged left ventricle with MAD for any MR grade and adjusting for body size ($P \leq 0.002$ for all), with no difference in LVEF (Supplemental Table 4). Furthermore, mitral dimensions in patients with MAD compared with those without MAD, stratified by bileaflet prolapse, showed longer and thicker leaflets and more mitral annular dilatation with MAD, irrespective of prolapse type and MR severity ($P \leq 0.02$ for all) (Supplemental Table 5).

LONG-TERM OUTCOME AFTER DIAGNOSIS. Total follow-up was 10.3 ± 3.0 years, during which 58 patients died (51 [12%] without MAD and 7 [4%] with MAD), and 170 had clinical arrhythmic events (159 had VT on Holter monitoring, 14 had VT or PVC ablation, 14 underwent ICD implantation, and there were 3 sudden deaths, including multiple events). Electrocardiographic and Holter characteristics are detailed in Supplemental Table 6. Mitral valve surgery was ultimately performed in 183 patients (31%) (93% repair, 7% replacement), including 63 with MAD (**Figure 2E**). Among those undergoing surgery, postoperative echocardiography showed absence of MAD in 100% of patients without preoperative MAD and 93% with preoperative MAD (**Figure 2F**).

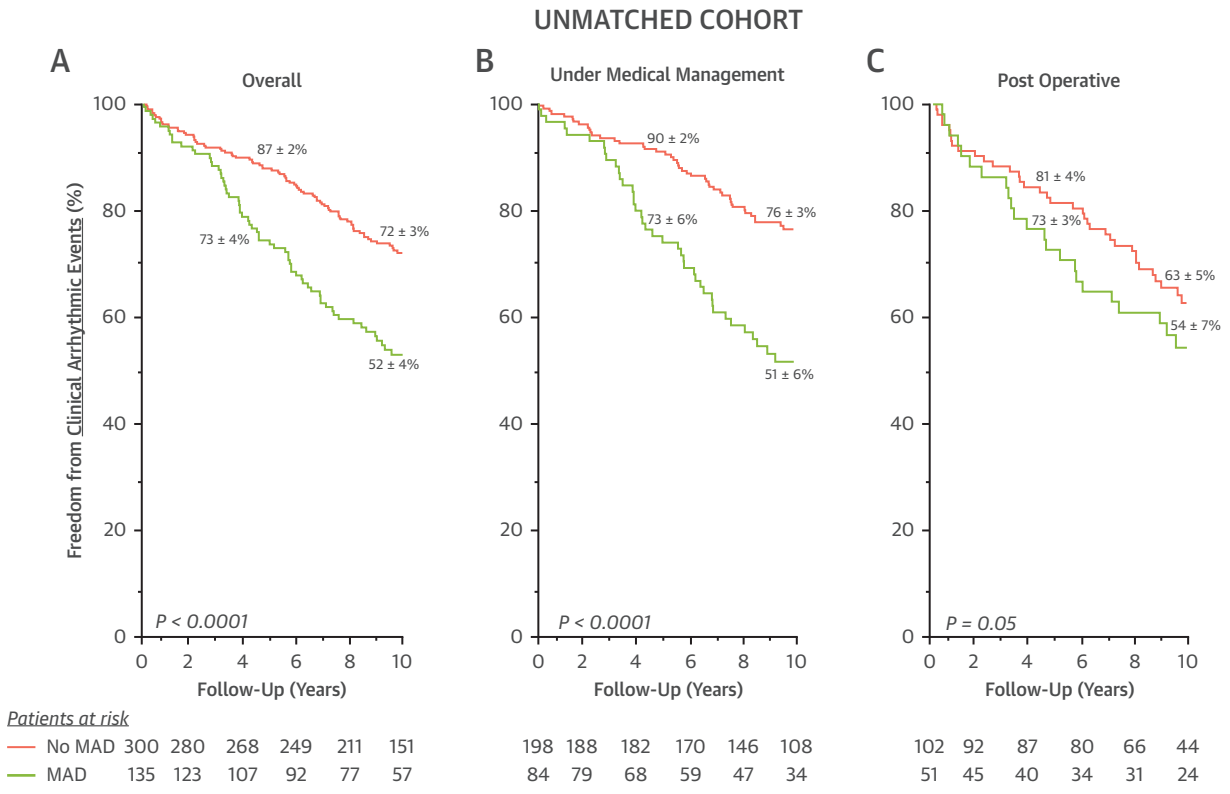
OVERALL SURVIVAL. Overall survival throughout follow-up was 96% ± 1% at 5 years and 89% ± 1% at 10 years. Ten-year survival was 97% ± 1% for patients with MAD and 86% ± 2% for those without MAD, concordantly with marked baseline differences, particularly age. After adjustment for age, sex, and Charlson index, no difference in survival between patients with MAD and those without MAD could be detected ($P = 0.10$). Further adjustment by symptoms, atrial fibrillation, LVEF, and MR grade showed similar results ($P = 0.30$) (**Table 3**).

In the matched cohort with similar age at baseline, survival was 98% ± 1% at 5 years and 95% ± 1% at 10 years. Ten-year survival was 97% ± 1% and 93% ± 2% in patients with MAD and those without MAD ($P = 0.40$) (**Figure 3**). Cox proportional hazards analysis showed no excess mortality associated with MAD (univariate HR: 0.64; 95% CI: 0.25-1.66; $P = 0.40$ for MAD vs no MAD). Adjusting for residual differences in left ventricular end-systolic diameter, bileaflet MVP, leaflet redundancy, and MR grade did not reveal differences in survival between patients with MAD and those without MAD (adjusted HR: 1.20; 95% CI: 0.40-3.58; $P = 0.80$). Adding time-dependent mitral surgery to the model, MAD was not independently associated with excess mortality (adjusted HR: 0.65; 95% CI: 0.24-1.71; $P = 0.60$).

Although patients with previous ICDs were excluded (2% of the cohort) because of potential immortal time bias, interrogations indicated no cardiac arrest (VF or sustained VT) episodes or appropriate discharges, and their inclusion would not have altered the lack of excess mortality with MAD ($P = 0.30$).

ARRHYTHMIC EVENTS DURING FOLLOW-UP. Freedom from arrhythmic event (VT 30 days after

FIGURE 4 **Impact on Arrhythmic Event-Free Survival of MAD in Overall Cohort**



Survival free of clinical and arrhythmic events stratified by mitral annular disjunction (MAD) in overall cohort **(A)** and for arrhythmia recording under medical management **(B)** or postoperative **(C)**. Note the substantial reduction in arrhythmic event-free survival with presence of MAD. Values are estimated survival ± SE.

diagnosis, ventricular arrhythmia ablation, ICD implantation, sudden cardiac death) (Figure 1) was 83% ± 2% at 5 years and 66% ± 2% at 10 years. Freedom from arrhythmic events was lower with MAD, 87% ± 2% in patients without MAD compared with 73% ± 4% in those with MAD at 5 years and 72% ± 3% and 52% ± 4%, respectively, at 10 years ($P < 0.0001$) (Figure 4A). In univariate Cox proportional hazards analysis, MAD was strongly associated with arrhythmic event occurrence (univariable HR: 2.16; 95% CI: 1.59-2.92; $P < 0.0001$) (Table 3).

Adjustment for age, sex, and comorbidity index did not affect this powerful association (adjusted HR: 2.45; 95% CI: 1.78-3.36; $P < 0.0001$ vs no MAD). Adjusting additionally for mitral characteristics (symptoms, MR grade, atrial fibrillation, and LVEF), MAD remained highly associated with arrhythmic events during follow-up (adjusted HR: 2.60; 95% CI: 1.87-3.62; $P < 0.0001$) (Table 3).

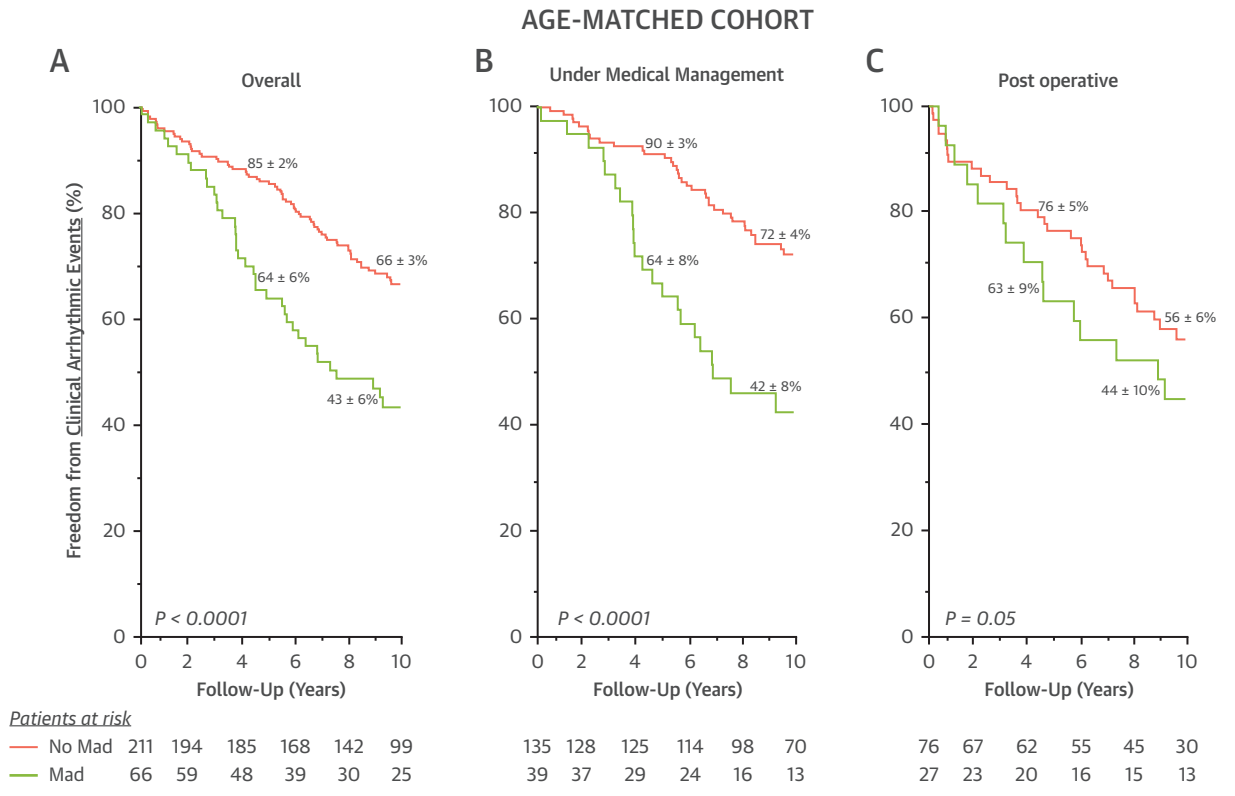
Stratifying by management phase (medical or surgical), MAD remained strongly associated with arrhythmic events under medical management (Figure 4B) (adjusted HR: 3.21; 95% CI: 2.03-5.06; $P < 0.0001$) (Table 3), with a weaker association after mitral surgery (Figure 4C, Table 3), but the interaction with Holter timing was insignificant ($P \geq 0.20$).

Stratified by age, patients ≤45 years of age (n = 89 [15% of the cohort]) tended to experience more ventricular arrhythmia ablation (6% vs 2%; $P = 0.05$) than older patients but no excess VT, ICD implantation, or sudden cardiac death ($P \geq 0.10$ for all).

MAD was associated with more severe arrhythmia (VT ≥180 beats/min) late after diagnosis (Supplemental Figure 1) even after adjustment (HR: 3.14; 95% CI: 1.60-7.29; $P = 0.002$). Accounting for time-dependent mitral surgery, MAD association with arrhythmic events persisted (adjusted HR: 2.54; 95% CI: 1.84-3.50; $P < 0.0001$), but VT risk after surgery did not reach significance (adjusted HR: 1.49; 95% CI: 0.73-3.04; $P = 0.30$)

In matched subsets, 122 patients had events recorded (Figure 1), and freedom from arrhythmic

FIGURE 5 Impact on Arrhythmic Event-Free Survival of MAD In Age-Matched Cohort



Survival free of clinical and arrhythmic events stratified by mitral annular disjunction (MAD) **(A)** and recorded under medical management **(B)** or postoperative **(C)** of age-matched cohort. Values are estimated survival ± SE.

events was 80% ± 2% at 5 years and 61% ± 3% at 10 years and was lower with MAD (43% ± 6% vs 66% ± 3%) at 10 years ($P < 0.0001$) (Figure 5). Cox proportional hazards analysis showed a strong and independent link between clinical arrhythmic events and MAD (univariate HR: 2.31; 95% CI: 1.59-3.35; $P < 0.0001$). Adjusting for residual differences in left ventricular end-systolic diameter, bileaflet MVP, leaflet redundancy, and MR grade did not affect this independent association (adjusted HR: 1.93; 95% CI: 1.22-3.05; $P = 0.005$). Stratifying by Holter timing, MAD remained strongly associated with arrhythmic events under medical management (Figure 5B) (adjusted HR: 2.10; 95% CI: 1.12-3.92; $P = 0.02$) but tended to lose significance after mitral surgery (adjusted HR: 1.91; 95% CI: 0.95-3.83; $P = 0.07$) (Figure 5C).

Further survival analysis on the basis of arrhythmia diagnosis as index time (ie, at Holter performance vs at MVP diagnosis) with follow-up from that time forward showed after VT excess mortality, which was delayed (4.4 ± 2.7 years after arrhythmia), 22% ± 4% at 5 years versus 13% ± 3% without VT ($P < 0.0001$) (adjusted HR: 2.09; 95% CI: 1.36-3.21; $P = 0.0008$). Independent VT association with excess mortality persisted as a time-dependent variable starting from MVP diagnosis (adjusted HR: 3.24; 95% CI: 2.60-4.66; $P < 0.0001$).

DISCUSSION

The present study, by gathering a large cohort of patients with isolated MVP, quite unique by its extensive echocardiographic and rhythmic characterization, provides robust power to assess MAD prevalence, phenotypic context, and independent impact on outcome. First, MAD is common at MVP diagnosis, detectable in 3 of 10 patients, generally relatively young. Advanced myxomatous degeneration, denoted by marked leaflet redundancy and bileaflet MVP, was the strongest MAD-associated MVP feature, independent of all baseline

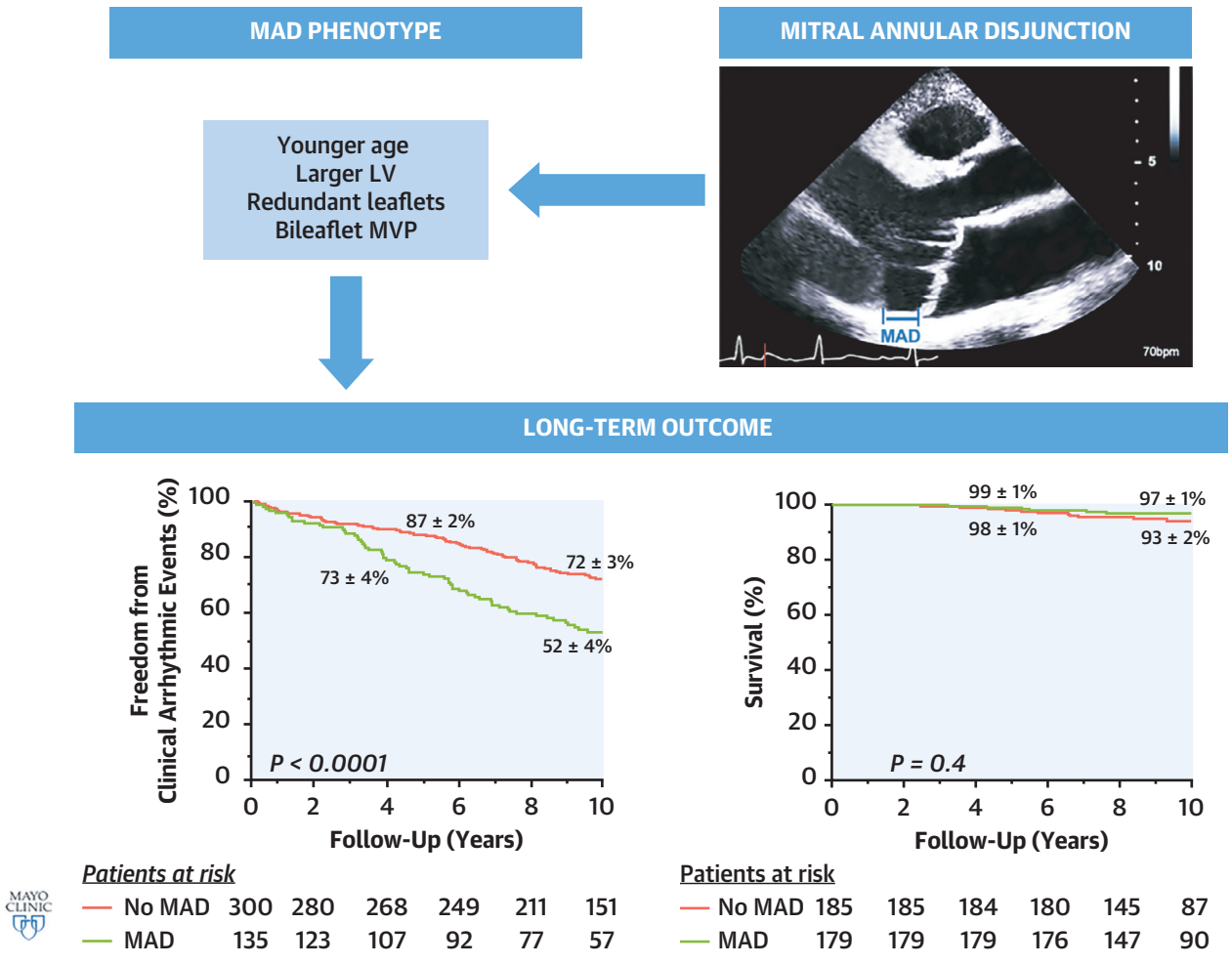
characteristics, whereas MR severity was not. These features were strongly associated with MAD after matching, particularly for age. In turn, MAD is associated with LV enlargement in excess of that justified by MR complicating MVP and with more redundant leaflets independently of bileaflet MVP presence. During follow-up, the main outcome, observed with any adjustment, is that MAD at MVP diagnosis is independently associated in the long term with excess occurrence of clinical arrhythmic events. However, arrhythmia incidence is progressive over time, and during the first 10 years following MVP diagnosis, MAD is not associated with excess mortality. In light of these results based on this first large and comprehensive cohort (**Central Illustration**), MAD diagnosis with isolated MVP should lead to careful detection of ventricular arrhythmias at diagnosis and during follow-up, but absence of excess mortality over a significant time frame should yield reassurance and avoidance of uncontrolled therapeutic interventions. Well-designed clinical trials should be conducted to evaluate the efficacy of electrophysiological and surgical therapies aiming at improving outcomes of MAD associated with MVP.

HETEROGENEITY OF MVP AND MAD. MVP is frequent and exhibits heterogeneous phenotypes, evident on the basis of the leaflet affected (29), occasionally with bicuspid aortic valve or with flail segments at diagnosis in about 15% of patients with isolated MVP (30), potentially linked to various metabolic expressions (31). Heterogeneity affects leaflets' length and thickness, variably increased (1) and concordant (32). Although MVP is often categorized as fibroelastic versus generalized myxomatous disease (33), there is a wide range of intermediate forms. Moreover, MR itself varies from absent to severe according to chordal elongation or rupture and annular enlargement. Morphologic MVP heterogeneity is apparent between sexes (34), and ages, more extensive in elderly patients (35), or with early familial MVP forms in the young, X-linked in some forms (36).

MAD phenotype, as shown in our study, is part of MVP morphologic and functional heterogeneity and, although frequent, affects only a fraction of MVP carriers. However, MAD occurrence is not random and is linked to the presence of advanced myxomatous disease, characterized by marked leaflet redundancy and bileaflet prolapse. Although in pathologic studies, MAD was linked to "floppy valves" (8) and frequently to severe myxomatous disease, there are to date no established MAD phenotype-genotype links, which are complex to investigate. On the basis of the framework phenotype-genotype of MVP associated with filamin-A (37), new studies are warranted to uncover genotypic characteristics related to MAD (38). Whether novel candidate cardiomyopathy-linked genes for MVP may explain MAD "disproportionate" LV remodeling and arrhythmic MVP (19,39) is conjectural (40), but our large study, demonstrating over time ventricular arrhythmia development with MAD, provides crucial new insights into MVP and MAD outcomes.

CLINICAL CONSEQUENCES AND OUTCOMES OF MAD. With MAD, the left ventricle is enlarged, in excess of MR caused by MVP and not related to age. This association (although causality remains to be established) is understood as consequential to deanchoring of the annulus and the left ventricle (11), with inefficient ventricular contraction and increase in end-systolic LV dimensions, which may have outcome implications (41). Whether such enlargement warrants modification of surgical indications is uncertain. Findings on clinical outcomes attached to MAD within the MVP complex are most novel and relevant to clinical practice. Lately, MAD has been painted as an ominous sign (22), with particular emphasis on severe arrhythmia, particularly sudden death (13,19–21), mentioned in early reports of sudden death with isolated MVP (9). It is a subject of great concern in managing patients with MVP (21,22). The association of MVP with severe ventricular arrhythmias is suggested by the origin of ectopic activity (20) but also by histopathologic and cardiac magnetic resonance examinations demonstrating LV fibrosis of papillary muscles and the inferobasal LV wall, often associated with MAD (19,42). Studies linking MAD and arrhythmias suffer from limited size, inconsistent populations with or without MVP, and particularly from cross-sectional designs (20) prone to bias. A much higher level of causality link requires outcome studies, which in our large cohort demonstrates that patients with isolated MVP are much more prone to develop arrhythmia if the MVP complex includes MAD, independently of all characteristics (39). Hence, our study shows clearly that MAD, over time and probably through a pathophysiological mechanism of progressive mitral apparatus fibrosis (13,14,19), contributes strongly and independently to arrhythmic MVP occurrence (39). However, arrhythmia incidence is progressive, delayed in most cases, and isolated MAD diagnosis should not lead clinicians to consider all patients at imminent risk for sudden death. This tempered approach is confirmed by the absence of excess

CENTRAL ILLUSTRATION **Mitral Annular Disjunction Phenotype and Outcome in Degenerative Mitral Regurgitation**



Essayagh, B. et al. J Am Coll Cardiol Img. 2021;14(11):2073-2087.

(Top right) Transthoracic echocardiographic long-axis view in end-systole displaying mitral valve prolapse with mitral annular disjunction (MAD). **(Top left)** MAD phenotype. **(Bottom left)** Lower arrhythmic event-free survival with presence of MAD. **(Bottom right)** Comparable survival of matched cohort stratified by MAD.

mortality over first 10 years following MVP diagnosis. This crucial fact demonstrated by long-term follow-up of our cohort should also lead clinicians to reassure most patients that MAD is not, in isolation, an immediate harbinger of sudden death. This is coherent with our observation that mortality after arrhythmia occurrence is fortunately inconsistently observed and is delayed late after arrhythmia diagnosis.

From monitoring and therapeutic points of view, few facts are available. With the now established link between MVP with MAD and future serious ventricular arrhythmias (39), it is intuitive that monitoring for arrhythmias should be more thorough, at least by regular Holter monitoring with detailed evaluation of arrhythmias (20). Utility of indwelling electrophysiological studies and ablation cannot be established by our cohort and will require clinical trials. With mitral surgery, we can establish complete postoperative MAD disappearance in almost all patients (12), probably because of suture of ring and prosthesis, joining the annulus to the LV myocardium, and collapsing the MAD gap. This annular correction does not occur with transcatheter edge-to-edge mitral repair. Whether preference should be given to surgical repair in patients with substantial MR appears logical but is not established yet. The benefit of mitral surgery indicated by life-threatening ventricular arrhythmia (43)

and electrophysiological ablation cannot be affirmed without a clinical trial.

STUDY LIMITATIONS. Although we retrospectively identified our cohort, patients were diagnosed consecutively, and their characteristics, (clinical, echocardiographic, and electrocardiographic) were prospectively measured, stored immediately, and retrieved electronically without modification. Measurements outside of routine practice (eg, MAD length) were obtained by experts (B.E., A.S.) blinded to outcomes. Holter recordings obtained for all (Holter numbers: 1.9 ± 1.7, median 1 [interquartile range: 1-2] per patient) were indicated by various circumstances and symptoms, not just palpitations and arrhythmias, minimizing bias in defining arrhythmia incidence. Patients undergoing Holter monitoring were representative of all those with MVP diagnosed during the same period (n = 6,068) with comparable age, sex, and ejection fractions ($P > 0.80$). Inclusion of CAD and history of myocardial infarction may be criticized, but they are part of the Charlson comorbidity index for comprehensive adjustment and did not affect the independent link of MAD to ventricular arrhythmia. Also, arrhythmias displayed no link to smoking, myocardial infarction, coronary stenting, or bypass grafting ($P \geq 0.07$ for all), to regional wall motion abnormalities or wall motion score index ($P \geq 0.50$), and to obstructive CAD by angiography when performed ($P = 0.40$). Because LV volume measurement may be technically complex with MAD (44), we focused on LV diameters, which demonstrated LV enlargement with MAD throughout the cardiac cycle. In that regard, for the detection of myocardial fibrosis linked with arrhythmia, future systematic studies of MAD may include cardiac magnetic resonance, currently not part of recommended MVP evaluation (23,45). Sudden death is fortunately rare, difficult to define consistently among all deaths, and would require a massive cohort and follow-up, while overall mortality includes such cases and is most robust. The trend toward lower incidence of ventricular arrhythmias after surgery suggests that future clinical trials should evaluate the efficacy of electrophysiological and surgical therapies as well as mitral surgery on arrhythmic outcomes of MAD associated with MVP.

CONCLUSIONS

The present large cohort demonstrates that MAD is frequent at MVP diagnosis and occurs most commonly with marked leaflet redundancy and bileaflet MVP suggestive of advanced myxomatous degeneration. Although MR severity is not associated with MAD, excess LV enlargement is present. MAD presence with MVP is associated with progressive excess incidence of clinical arrhythmic events and VT after diagnosis. However, this association is progressive and not linked to excess mortality within the first 10 years post-diagnosis. Hence, although reassurance is in order for mortality, careful monitoring for occurrence of ventricular arrhythmias is warranted. and clinical trials to test arrhythmia therapies should be designed.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

The notable prevalence of MAD in this large cohort of patients with isolated MVP emphasizes the need to diagnose this morphologic and functional abnormality in routine practice and to contextually analyze its unique phenotype of redundant leaflets and bileaflet MVP. The independent link with long-term excess incidence of clinical arrhythmic events suggest that monitoring for arrhythmia should be performed and repeated. However, despite the reference to MAD as a "red flag" for sudden death, the observation that within the first 10 years post-diagnosis MAD is not linked to excess mortality should lead to reassurance in most cases, with careful follow-up.

TRANSLATIONAL OUTLOOK: MAD is part of the heterogeneity of MVP, and new studies are warranted to uncover potential underlying biochemical and genotypic characteristics related to MAD. Clinical trials to test monitoring and therapeutic approaches for MAD-related ventricular arrhythmias should be designed to improve clinical outcomes in patients with MVP.

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KEY WORDS mitral annular disjunction, mitral regurgitation, mitral valve prolapse, outcome, ventricular arrhythmia

APPENDIX For supplemental tables and figures and extended discussion of study strengths and limitations, please see the online version of this paper.