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# Presentation and Outcome of Arrhythmic Mitral Valve Prolapse

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## ABSTRACT

**BACKGROUND** Mitral valve prolapse (MVP) is often considered benign but recent suggestion of an arrhythmic MVP (AMVP) form remains incompletely defined and uncertain.

**OBJECTIVES** This study determined ventricular arrhythmia prevalence, severity, phenotypical context, and independent impact on outcome in patients with MVP.

**METHODS** A cohort of 595 (age 65 ± 16 years; 278 women) consecutive patients with MVP and comprehensive clinical, arrhythmia (24-h Holter monitoring) and Doppler-echocardiographic characterization, was identified. Long-term outcomes were analyzed.

**RESULTS** Ventricular arrhythmia was frequent (43% with at least ventricular ectopy ≥5%), most often moderate (ventricular tachycardia [VT]; 120 to 179 beats/min) in 27%, and rarely severe (VT ≥180 beats/min) in 9%. Presence of ventricular arrhythmia was associated with male sex, bileaflet prolapse, marked leaflet redundancy, mitral annulus disjunction (MAD), a larger left atrium and left ventricular end-systolic diameter, and T-wave inversion/ST-segment depression (all $p \leq 0.001$). Severe ventricular arrhythmia was independently associated with presence of MAD, leaflet redundancy, and T-wave inversion/ST-segment depression (all $p < 0.0001$) but not with mitral regurgitation severity or ejection fraction. Overall mortality after arrhythmia diagnosis (8 years; 13 ± 2%) was strongly associated with arrhythmia severity (8 years; 10 ± 2% for no/trivial, 15 ± 3% for mild and/or moderate, and 24 ± 7% for severe arrhythmia; $p = 0.02$). Excess mortality was substantial for severe arrhythmia (univariate hazard ratio [HR]: 2.70; 95% confidence interval [CI]: 1.27 to 5.77; $p = 0.01$ vs. no/trivial arrhythmia), even after it was comprehensively adjusted, including for MVP characteristics (adjusted HR: 2.94; 95% CI: 1.36 to 6.36; $p = 0.006$) and by time-dependent analysis (adjusted HR: 3.25; 95% CI: 1.56 to 6.78; $p = 0.002$). Severe arrhythmia was also associated with higher rates of mortality, defibrillator implantation, VT ablation (adjusted HR: 4.68; 95% CI: 2.45 to 8.92; $p < 0.0001$), particularly under medical management (adjusted HR: 5.80; 95% CI: 2.75 to 12.23; $p < 0.0001$), and weakly post-mitral surgery (adjusted HR: 3.69; 95% CI: 0.93 to 14.74; $p = 0.06$).

**CONCLUSIONS** In this large cohort of patients with MVP, ventricular arrhythmia by Holter monitoring was frequent but rarely severe. AMVP was independently associated with phenotype dominated by MAD, marked leaflet redundancy, and repolarization abnormalities. Long-term severe arrhythmia was independently associated with notable excess mortality and reduced event-free survival, particularly under medical management. Therefore, AMVP is a clinical entity strongly associated with outcome and warrants careful risk assessment and well-designed clinical trials.
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**ABBREVIATIONS AND ACRONYMS**

**AMVP** = arrhythmic mitral valve prolapse

**CI** = confidence interval

**ECG** = electrocardiography

**HR** = hazard ratio

**ICD** = implantable cardioverter-defibrillator

**LAVI** = left atrium volume index

**LVEF** = left ventricular ejection fraction

**MAD** = mitral annular disjunction

**MR** = mitral regurgitation

**MVP** = mitral valve prolapse

**OR** = odds ratio

**PVC** = premature ventricular complex

**SCD** = sudden cardiac death

Mitral valve prolapse (MVP), the most prevalent valve condition in Western countries, affects approximately 2.4% of the population (1,2). The outcome of MVP is mostly determined by presence and severity of mitral regurgitation (MR) and its consequences (3,4). Thus, when severe MR is present, prompt surgical repair is most often recommended to restore life expectancy (3,5), whereas with lesser MR consequences, MVP is considered relatively benign, and, overall, has been demonstrated to enjoy excellent survival (2,6). However, reports of sudden cardiac death (SCD) (7,8) and ventricular arrhythmia (9) in MVP with MR (10) or apparently uncomplicated, raised the concern that an MVP subset, independent of the degree of MR, may not be benign and may incur a higher risk of arrhythmia and possible mortality.

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Case report studies with a limited number of patients described occurrence of SCD in isolated MVP (11–13). Because of the case reports' disparate nature, it was uncertain whether SCD was directly linked to MVP or was incidental and unrelated. Recently, a meta-analysis (14), along with a larger report of SCD cases (15), was more suggestive of a link between SCD and MVP, independent of severe MR or left ventricular (LV) dysfunction, and was characterized by specific MVP features, which suggested that an arrhythmic MVP (AMVP) phenotype might be contributing ultimately to SCD (16,17).

However, confusion persists regarding potential AMVP characteristics. Some studies have suggested that bileaflet MVP is central to the AMVP phenotype (12,14,18). However, this suggestion was based on limited data (12,14,18), and it remains controversial that bileaflet MVP would be a marker of excess mortality (19) and arrhythmia, in view of its high prevalence and benign outcome in epidemiological studies (20). Another morphological abnormality, mitral annulus disjunction (MAD), has been suggested as a possible link to ventricular arrhythmia with MVP (21,22), but other studies have indicated that MAD could be present without concomitant MVP or arrhythmias (23,24). Therefore, clinical, morphological, and electrophysiological characteristics of a potential AMVP phenotype are uncertain. Its potential link to outcomes due to the small size of previous clinical studies and to absent cohorts that involved comprehensive characterization and long-term follow-up are even more unsubstantiated.

To resolve these gaps of knowledge, a large cohort of patients with MVP with comprehensive characterization of arrhythmias by electrocardiography (ECG) and 24-h Holter monitoring, extensive records of symptoms, clinical characteristics and comorbidities, detailed Doppler echocardiographic features, and long-term follow-up is required. For the first time, we gathered such a cohort to determine ventricular arrhythmia prevalence, severity, and its link to specific MVP characteristics, and to examine the hypothesis that severe ventricular arrhythmia is independently associated with outcomes.

## METHODS

To define the prevalence and significance of arrhythmias in all types of MVP, all eligible consecutive patients: 1) had to be age 18 years or older; 2) diagnosed with isolated MVP, with or without flail leaflet, and first diagnosed at the Mayo Clinic (Rochester, Minnesota) from 2003 to 2011; 3) had a comprehensive clinical and echocardiographic evaluation at diagnosis, including symptoms, clinical history, and comorbidities; 4) had a comprehensive rhythmic evaluation on 24-h Holter monitoring; 5) had to have available images for morphological echocardiographic detailed measurements; and 6) had to have absence of arrhythmic cardiomyopathy diagnosed at our electrophysiology tertiary laboratory (arrhythmogenic right ventricular cardiomyopathy, long-QT syndrome, arrhythmogenic-dilated cardiomyopathy, or Lamin-A/C cardiomyopathy). Subjects were excluded if they denied research authorization (per Minnesota law) or presented with any of the following: 1) moderate or more than moderate aortic regurgitation or stenosis; 2) moderate or more than moderate mitral stenosis; 3) previous valvular surgery; 4) congenital heart disease (patent foramen ovale was not excluded); and 5) hypertrophic and restrictive cardiomyopathies or constrictive pericarditis. Because these were low-risk patients, the written consent requirement was waived by the Mayo Clinic Institutional Review Board, which approved this study.

**ECHOCARDIOGRAPHIC EVALUATION.** Comprehensive Doppler echocardiography followed the Mayo Clinic standard imaging protocol, under direct supervision of the Mayo consultant in routine practice, using standardized guidelines (25). Integrative grading of degenerative MR used specific, supportive, and quantitative (if possible) measures to classify degenerative MR as absent to severe according to guidelines. All standard measurements were performed at diagnosis and downloaded from the digital

echocardiographic repository without alteration. Nonstandard measurements of mitral leaflets length and/or thickness, of leaflet redundancy and severity, and of the presence of MAD and maximum MAD length were performed by an experienced echocardiography specialist on digitally stored images without knowledge of arrhythmia characteristics and outcomes. Leaflet length and/or thickness was measured during diastole in the parasternal long-axis view. Leaflet redundancy was graded by evaluating excess valve tissue, whereas thickening was graded semi-quantitatively (7,26). MAD distance was measured in the parasternal long-axis view at end-systole and was defined as the distance between the mitral annulus and the systolic bulge of the ventricular myocardium (21).

**ELECTROCARDIOGRAPHIC EVALUATION.** All standard ECG measurements were downloaded from a digital ECG repository without alteration. Nonstandard measurements were performed by an electrophysiologist blinded to all clinical, echocardiographic, and/or outcome data. The 24-h Holter review involved full-tracings and baseline heart rhythm, heart rate, presence and burden of premature ventricular complexes (PVCs) per 24 h. The number, average beats, rate, and duration of ventricular tachycardia (VT) were noted. QRS duration and the shortest coupling interval of dominant PVCs were also measured. Origin of ventricular ectopy was determined when captured by 3- or 12-lead Holter monitoring, using validated criteria (27-29) when the PVC burden was ≥1% or with VT events. Baseline ECG characteristics included QRS duration and/or morphology, QT and/or QTc intervals, ST-segment depression, T-wave inversion, and J-point elevation. Burden and complexity of ventricular arrhythmias were graded as previously recommended (30-33), as the following: no/trivial with no VT and PVC frequency below median (<5%) (30); mild with PVCs above the median (≥5%) and/or with documented VT runs no faster than 120 beats/min (34); moderate with VT runs of 120 to 179 beats/min; and as severe with VT ≥180 beats/min and/or proven history of VT/ventricular fibrillation (VF), indicating a need for an implantable cardioverter-defibrillator (ICD) (31,32).

**DEMOGRAPHIC AND CLINICAL DATA.** Demographic and clinical data were extracted electronically from patients' medical records, including age, sex, body mass index, vital signs, comorbidities (summated by Charlson-index). History of VT/VF with ICDs was retrieved. Symptoms (chest pain, dyspnea, syncope, palpitations, and edema) were systematically collected from clinical notes using natural language processing.

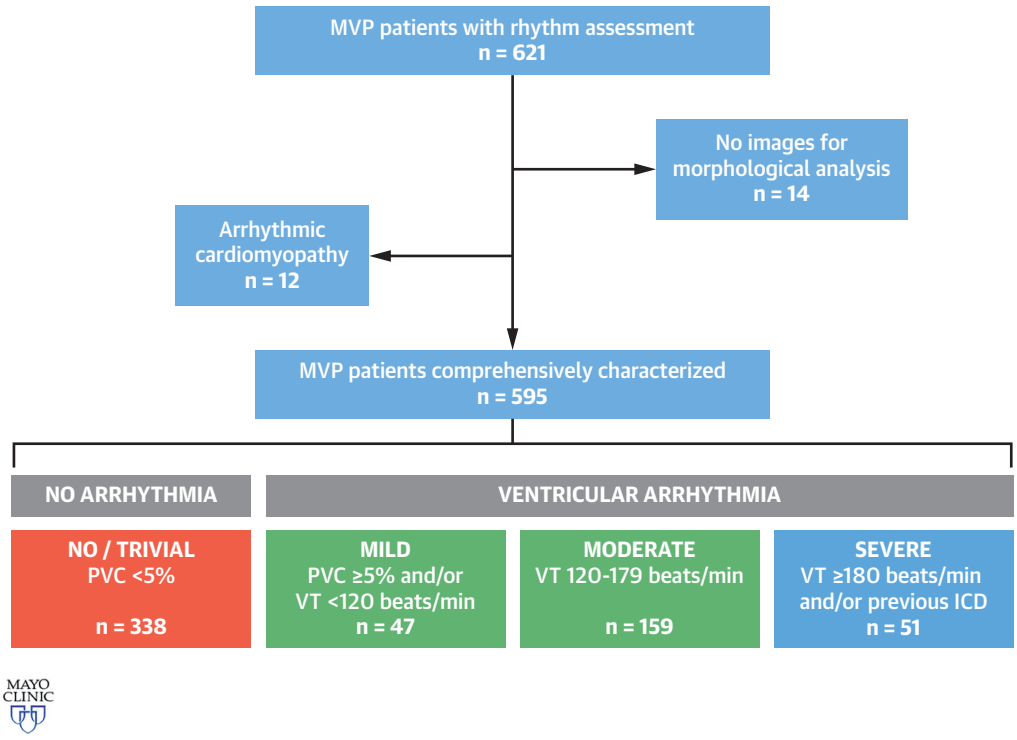
**FOLLOW-UP.** The primary outcome measure was overall survival, and the secondary endpoint was event-free survival, in which events were mortality, ICD placement, and VT ablation. Death occurrence and dates were obtained by Accurint (LexisNexis, New York, New York), a proprietary resource that gathers information from multiple national sources, including the Social Security Death Index, in the middle of 2019. To ensure accurate mortality counts, patients considered alive (based on information from Accurint) were censored on December 31, 2018. Because of legal restrictions, ascertainment of death causes, particularly SCD, was not possible and only overall mortality was analyzed.

**STATISTICAL ANALYSIS.** Results were expressed as mean ± SD, median (interquartile range), or percentages. Qualitative variables were compared using chi-square tests, and quantitative data were assessed using analysis of variance or Wilcoxon's test. Patients with no and/or trivial ventricular ectopy formed the nonarrhythmic subset and were compared with patients with arrhythmia as a whole and with graded arrhythmia severity.

Characteristics associated with ventricular arrhythmia and severity were assessed by logistic regression using patient, MVP, and ventricular characteristics: age, left atrial volume index (LAVI), LV end-systolic diameter (LVESD), T-wave inversion/ST-segment depression, ECG QTc interval, bileaflet and/or single leaflet prolapse, leaflet redundancy, MAD, and MR grade. Because mitral leaflets length and/or thickness (as continuous and categorical) and leaflet redundancy were highly correlated ($p < 0.0001$), only leaflet redundancy grading was included in the models. Odds ratios (ORs) for the presence of ventricular arrhythmia (vs. no arrhythmia) and of severe ventricular arrhythmia (vs. moderate and no/mild) were reported for each independent determinant, unadjusted, and in multivariable analysis. To avoid overfitting in the model that predicted severe ventricular arrhythmia, a limited number of potential determinants was allowed. Overall fitting of models was summarized using the C-statistic.

Event rates after Holter monitoring were estimated using the Kaplan-Meier method and compared using the log-rank test. Analysis was stratified by timing of Holter monitoring, as arrhythmia assessment under medical management if the rhythmic evaluation was performed with the native MVP, or post-operative arrhythmia assessment if the rhythmic evaluation was performed after mitral repair and/or replacement. For outcome analysis, patients with a history of VT/VF

**FIGURE 1** Study Population Flowchart




Sequence of eligibility led to a cohort of 595 patients with mitral valve prolapse (MVP) with arrhythmia assessment. ICD = implantable cardioverter-defibrillator; PVC = premature ventricular complex; VT = ventricular tachycardia.

and a previous ICD were excluded. Cox proportional hazard regression models that analyzed the association of ventricular arrhythmia with outcome were adjusted for age, sex, comorbidity index, LV ejection fraction (LVEF), MR grade, and MAD incrementally. To verify the impact of the effect of severe ventricular arrhythmia on outcome, it was also analyzed as a time-dependent covariate from the first MVP diagnosis. Hazard ratios (HRs) are presented with 95% confidence intervals. A p value $<0.05$ was considered significant.

## RESULTS

**BASELINE CHARACTERISTICS.** Among 621 patients with MVP and comprehensive rhythm characterization, 14 were excluded due to lack of digital echocardiographic images, and 12 were excluded due to arrhythmogenic right ventricular cardiomyopathy (n = 7), arrhythmogenic-dilated cardiomyopathy (n = 2), or Lamin-A/C cardiomyopathy (n = 3) (Figure 1). Baseline demographic and/or clinical characteristics of the enrolled 595 patients (278 women; age 65 ± 16 years) in the final cohort are summarized in Table 1. Clinically, 11% had history of syncope, 18% had atrial fibrillation, and 23% had coronary artery disease with a low comorbidity index of 0.84 ± 1.10. By echocardiography, LV dilatation was mild on average (25), the LVEF was 62 ± 7%, and the LAVI was 44 ± 21 ml/m$^2$. Morphologically, bileaflet prolapse was found in 280 patients (47%), flail leaflet in 60 (10%), leaflet-redundancy in 283 (48%), and MAD in 186 (31%), measuring 7.5 ± 2.8 mm. MR was severe in 28%, moderate in 28%, and mild in 8%, whereas 36% of patients had no or trivial MR. By ECG, T-wave inversion (20%), ST-segment depression (15%), or a early repolarization pattern (13%) was frequent, with 26% having combined T-wave inversion/ST-depression. By 24-h Holter examination, median PVC burden was 0.2% (interquartile range: 0% to 3%) of total beats/day, mostly a single PVC, and 230 patients (39%) had ventricular ectopic runs (7% with VT ≥180 beats/min). History of aborted SCD due to proven VT/VF, as indicated by an ICD, was found in 10 patients in the severe arrhythmia group. When ectopy origin identification was possible (76% of patients with ventricular arrhythmia on Holter

**TABLE 1 Baseline Characteristics**

| | Overall Population (N = 595) | No Arrhythmia (n = 338) | Ventricular Arrhythmia (n = 257) | p Value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Age, yrs | 65 ± 16 | 63 ± 17 | 68 ± 15 | 0.0001 |
| Female | 278 (47) | 178 (53) | 100 (39) | 0.0008 |
| BMI, kg/m$^2$ | 25 ± 5 | 25 ± 5 | 26 ± 5 | 0.0008 |
| HR, beats/min | 68 ± 14 | 67 ± 14 | 68 ± 15 | 0.40 |
| Atrial fibrillation | 107 (18) | 53 (16) | 54 (21) | 0.09 |
| Hypertension | 227 (38) | 119 (35) | 108 (42) | 0.09 |
| Diabetes | 43 (7) | 23 (7) | 20 (8) | 0.60 |
| Dyslipidemia | 242 (41) | 133 (39) | 109 (42) | 0.50 |
| CAD history | 135 (23) | 65 (19) | 70 (27) | 0.02 |
| Congestive heart failure history | 46 (8) | 19 (6) | 27 (11) | 0.03 |
| Charlson Index | 0.84 ± 1.10 | 0.78 ± 1.06 | 0.92 ± 1.14 | 0.10 |
| Symptoms | | | | |
| Syncope history | 66 (11) | 43 (13) | 23 (9) | 0.10 |
| Chest pain | 110 (18) | 69 (20) | 41 (16) | 0.20 |
| Palpitation | 213 (36) | 122 (36) | 91 (35) | 0.90 |
| Dyspnea | 210 (35) | 114 (34) | 96 (37) | 0.40 |
| Edema | 53 (9) | 28 (8) | 25 (10) | 0.50 |
| Echocardiographic variables | | | | |
| Bileaflet | 280 (47) | 141 (42) | 139 (55) | 0.003 |
| Posterior | 232 (39) | 139 (41) | 93 (36) | 0.03 |
| Flail leaflet | 60 (10) | 30 (9) | 30 (12) | 0.30 |
| MAD | 186 (31) | 74 (21) | 112 (44) | <0.0001 |
| MAD length, mm | 7.5 ± 2.8 | 6.6 ± 2.4 | 8.0 ± 3.0 | 0.001 |
| Mitral leaflets length, mm | | | | <0.0001 |
| Anterior | 22.7 ± 4.4 | 21.5 ± 4.0 | 24.1 ± 4.6 | |
| Posterior | 15.4 ± 4.2 | 14.1 ± 3.7 | 17.0 ± 4.1 | |
| Mitral leaflets proximal thickness, mm | | | | <0.0001 |
| Anterior | 2.3 ± 1.2 | 2.1 ± 0.7 | 2.6 ± 1.7 | |
| Posterior | 2.3 ± 0.9 | 2.1 ± 0.8 | 2.5 ± 1.0 | |
| Mitral leaflet redundancy | 283 (48) | 132 (40) | 151 (60) | <0.0001 |
| LVEDD, mm | 52 ± 7 | 50 ± 6 | 54 ± 7 | <0.0001 |
| Indexed LVEDD, mm/m$^2$ | 28 ± 4 | 27 ± 4 | 28 ± 4 | 0.005 |
| LVESD, mm | 33 ± 6 | 32 ± 5 | 35 ± 6 | <0.0001 |
| Indexed LVESD, mm/m$^2$ | 18 ± 3 | 17 ± 3 | 18 ± 3 | 0.004 |
| LVEF | 62 ± 7 | 63 ± 6 | 62 ± 8 | 0.03 |
| LAVI, ml/m$^2$ | 44 ± 21 | 38 ± 17 | 52 ± 24 | <0.0001 |
| MR | | | | <0.0001 |
| No/trivial | 215 (36) | 159 (47) | 56 (22) | |
| Mild | 47 (8) | 25 (7) | 22 (9) | |
| Moderate | 167 (28) | 79 (23) | 88 (34) | |
| Severe | 166 (28) | 75 (22) | 91 (35) | |
| ERO, mm$^2$ | 15 (0–29) | 9 (0–25) | 20 (8–34) | <0.0001 |
| RVol, ml | 25 (0–50) | 14 (0–42) | 34 (13–57) | <0.0001 |
| ECG and Holter characteristics | | | | |
| Corrected QT interval, ms | 441 ± 38 | 434 ± 36 | 450 ± 38 | <0.0001 |
| T-wave inversion/ ST-segment depression | 152 (26) | 54 (16) | 98 (39) | <0.0001 |
| T-wave inversion | 115 (20) | 42 (13) | 73 (29) | <0.0001 |
| ST-segment depression | 86 (15) | 29 (9) | 57 (23) | <0.0001 |
| J-point elevation | 74 (13) | 43 (13) | 31 (13) | 0.90 |
| Average HR, beats/min | 74 ± 13 | 73 ± 13 | 75 ± 13 | 0.03 |
| Minimum | 54 ± 11 | 53 ± 10 | 55 ± 11 | 0.05 |
| Maximum | 122 ± 46 | 122 ± 57 | 123 ± 26 | 0.90 |
| PVC duration, ms | 155 (143–167) | 161 (148–176) | 154 (141–168) | 0.80 |
| PVC coupling, ms | 478 (419–559) | 498 (427–551) | 475 (419–564) | 0.90 |

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

BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiography; EF = ejection fraction; ERO = effective regurgitant orifice; HR = heart rate; LAVI = left atrial volume index; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MAD = mitral annulus disjunction; MR = mitral regurgitation; PVC = premature ventricular complex; RVol = regurgitant volume.

**TABLE 2 MVP Characteristics Associated With Ventricular Arrhythmia Severity**

| Determinants of Ventricular Arrhythmia Severity | Severity Subgroups* | Univariate Analysis OR (95% CI) | p Value | Multivariate Analysis† OR (95% CI) | p Value |
|---|---|---|---|---|---|
| MAD | Mild/moderate | 1.04 (1.03–1.06) | 0.40 | 2.18 (0.89–2.94) | <0.0001 |
| | Severe | 3.27 (2.22–4.84) | <0.0001 | 6.97 (3.31–14.78) | <0.0001 |
| Redundant leaflets | Mild/moderate | 1.12 (0.98–1.17) | 0.001 | 1.72 (0.94–2.28) | 0.0001 |
| | Severe | 2.68 (1.82–3.98) | <0.0001 | 3.85 (1.90–7.85) | 0.0001 |
| T-wave inversion and/or ST-segment depression | Mild/moderate | 1.03 (0.97–1.04) | 0.60 | 2.30 (0.87–3.10) | <0.0001 |
| | Severe | 3.41 (2.28–5.12) | <0.0001 | 8.04 (3.85 –16.89) | <0.0001 |

*Versus no/trivial ventricular arrhythmia. †Adjusted for age, MAD, redundant leaflet, T-wave inversion/ST-segment depression.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

monitoring), it was mostly (66%) from the mitral apparatus (including the annulus and papillary muscle), with no differences in arrhythmia origin between severity subgroups ($p = 0.30$).

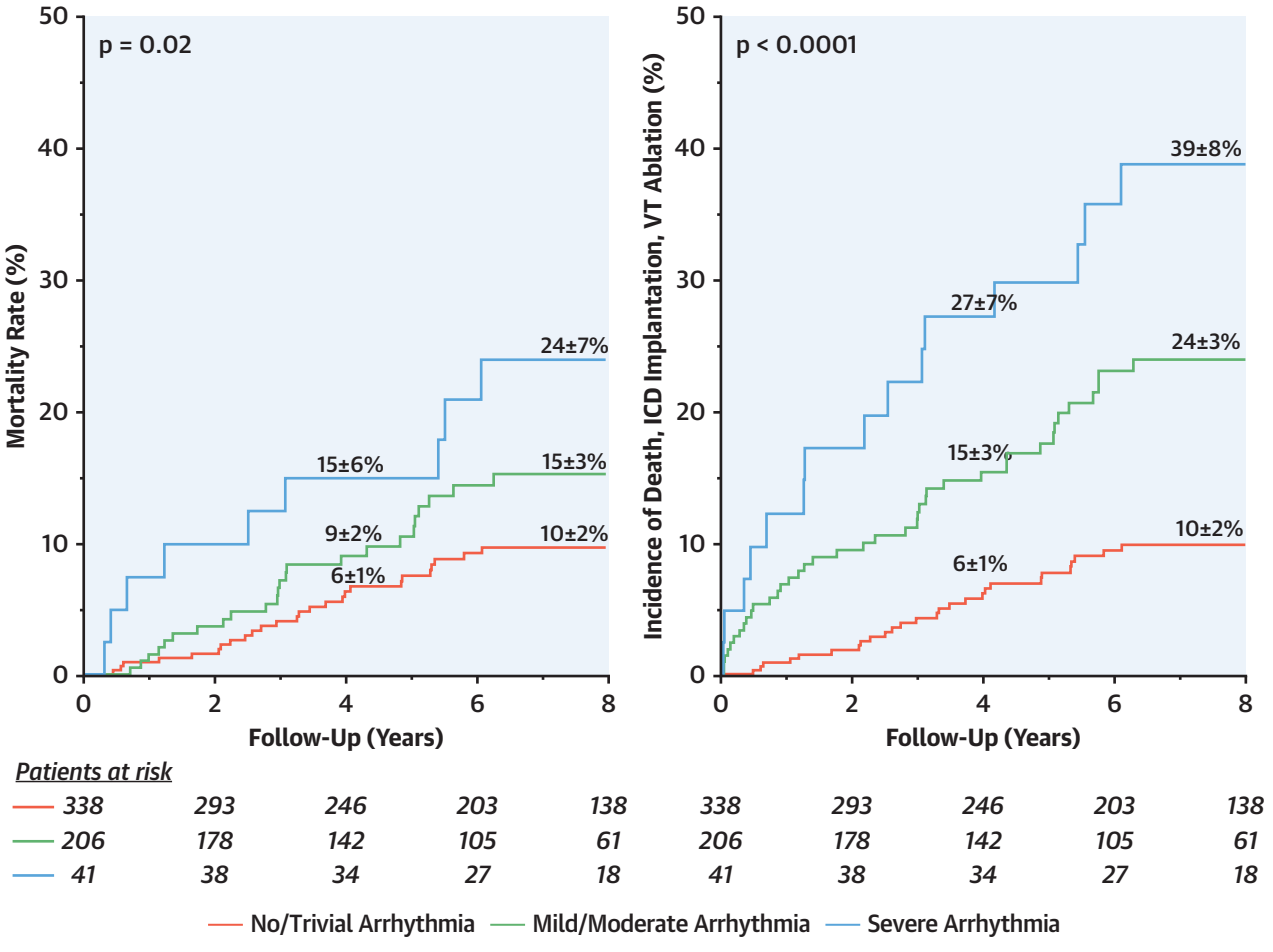
Stratified by arrhythmia assessment timing, baseline characteristics of the 441 patients with arrhythmia assessment under medical management were comparable to the overall cohort, with slightly lower MR grades. Patients with arrhythmia assessment post-operatively were older and had a lower comorbidity index, longer MAD, an enlarged LV, and more severe MR (Supplemental Tables 1A and 1B).

Comparison between groups (**Table 1**) characterized by presence of arrhythmia (≥5% PVC and/or VT) or absence of arrhythmia showed frequent ventricular arrhythmias (43%) were associated with male sex, with no difference in the comorbidity index or symptoms. Echocardiographically, the presence of arrhythmia was associated with more bileaflet prolapse, redundant leaflets, severe MR, presence of MAD of longer distance, a larger LAVI and LV, and a lower EF (all $p \leq 0.03$). Electrocardiographic QTc was longer in patients with ventricular arrhythmia with frequent T-wave inversion/ST-segment depression (all $p \leq 0.0001$). Stratified by timing of arrhythmia assessment (Supplemental Tables 1A and 1B), the comparison of arrhythmic and nonarrhythmic MVP showed similar characteristics and differences, although these were less significant post-operatively due to lower power. There was no interaction between Holter timing and arrhythmia presence in regard to clinical and echocardiographic characteristics (all $p > 0.18$). Also, Doppler echocardiographic data closest to the Holter monitoring data showed no significant change with regard to LV characteristics, LAVI, or MR in comparison to first MVP diagnosis (all $p > 0.05$) (Supplemental Table 1C).

Arrhythmia severity overall showed that 9% had severe ventricular arrhythmia (VT ≥180 beats/min and/or history of proven VT/VF that indicated a need for an ICD), 27% had moderate ventricular arrhythmia (VT 120 to 179 beats/min), 8% had mild ventricular arrhythmia (≥5% PVC and/or VT <120 beats/min), and 57% had no/trivial ectopy (<5% PVCs; median: 0.02% [interquartile range: 0% to 0.3%]) of total beats/day). With increasing arrhythmia severity, baseline characteristics differences were generally similar to the arrhythmia and/or no arrhythmia comparison (Supplemental Table 1D), although no link to older age, coronary artery disease, or regional wall motion abnormalities was noticed ($p > 0.05$) with severe arrhythmia. Conversely, with increasing arrhythmia severity, trends for more frequent bileaflet prolapse, MAD presence and length, increasing leaflet length and/or thickness and redundancy, greater LV and LA enlargement, and more ST-T changes were noted.

**CHARACTERISTICS ASSOCIATED WITH AMVP.** Clinical and/or echocardiographic characteristics associated with presence of ventricular arrhythmia are presented in Supplemental Table 2. Univariate analysis showed MAD, leaflet redundancy, and T-wave inversion/ST-segment depression emerging as the strongest predictors of ventricular arrhythmia, all remaining independently associated with moderate and strongly with severe arrhythmia (adjusted OR vs. no/trivial: 6.97; 95% CI: 3.31 to 14.78) for the presence of MAD, an OR of 3.85 (95% CI: 1.90 to 7.85) for leaflet redundancy, and an OR of 8.04 (95% CI: 3.85 to 16.89) for repolarization abnormalities (all $p < 0.0001$) (**Table 2**). Other independent predictors of the presence of ventricular arrhythmia were LAVI, LVESD, and ECG QTc, whereas sex, severe MR, and bileaflet prolapse were not predictors (model C-statistics = 0.79). Determinants of arrhythmia presence stratified by Holter timing confirmed robust associations of MAD and redundancy (as well as LA and LV characteristics) with arrhythmias detected under medical management, whereas these were more weakly noted for arrhythmias detected after mitral surgery (Supplemental Table 2).

**FIGURE 2** **Impact on Survival of Ventricular Arrhythmia Severity**




**(Left)** Mortality rate and **(right)** incidence of death, need for ICD, or VT ablation of MVP stratified by ventricular arrhythmia severity in overall cohort. Note the mortality difference with ventricular arrhythmia severity, which was considerable when severe. Abbreviations as in Figure 1.

**LONG-TERM OUTCOME AFTER HOLTER EXAMINATION.** During follow-up of 6.0 ± 3.0 years, 183 patients underwent mitral surgery; 59 died, 13 underwent ICD implantation, and 15 had VT ablation.

**OVERALL SURVIVAL.** Mortality throughout follow-up was 8 ± 1% at 4 years and 13 ± 2% at 8 years. Stratified by the presence of ventricular arrhythmia, 4- and 8-year overall mortality were 6 ± 1% and 10 ± 2% for the no arrhythmia group versus 10 ± 2% and 17 ± 3% for the ventricular arrhythmia group ($p = 0.02$). Univariately, the group with any ventricular arrhythmia had a notable HR for a mortality of 1.81 (95% CI: 1.09 to 3.03; $p = 0.02$), with a decreased significance after adjustment for age (adjusted HR: 1.45; 95% CI: 0.85 to 2.47; $p = 0.20$). Stratified by timing of Holter monitoring, a similar pattern of decreased significance after adjustment was noted under medical management or post-mitral surgery. Holter timing itself was insignificant without interaction with adjustment variables ($p \geq 0.16$).

Stratified by ventricular arrhythmia severity (Figure 2), overall mortality was remarkably different between groups. Overall survival rates (for 4 and 8 years) were, respectively, 6 ± 1% and 10 ± 2% for no arrhythmia, 9 ± 2% and 15 ± 3% for mild–moderate ventricular arrhythmia versus 14 ± 6% and 24 ± 7% for severe ventricular arrhythmia ($p = 0.02$). Cox proportional hazards analysis showed univariate HRs of 1.61 (95% CI: 0.93 to 2.81; $p = 0.09$) for mild–moderate ventricular arrhythmia and 2.70 (95% CI: 1.27 to 5.77; $p = 0.01$) for severe ventricular arrhythmia versus no arrhythmia. In multivariable

**TABLE 3 Outcome Implications of Ventricular Arrhythmia Stratified by Severity**

| | Distribution of Events by Arrhythmia | | | Hazard of Events According to Arrhythmia | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No/Trivial (n = 338) | Mild/ Moderate (n = 206) | Severe (n = 41) | Ventricular Arrhythmia* | | Mild/Moderate* | | Severe* | |
| Outcome | Events per 100 Patient-Years | | | Adjusted HR† (95% CI) | p Value | Adjusted HR† (95% CI) | p Value | Adjusted HR† (95% CI) | p Value |
| Overall mortality | 25 | 51 | 56 | 1.45 (0.85–2.47) | 0.20 | 1.20 (0.68–2.14) | 0.50 | 2.94 (1.36–6.36) | 0.006 |
| Overall mortality, ICD implantation, VT ablation | 25 | 80 | 89 | 2.66 (1.65–4.31) | <0.0001 | 2.27 (1.36–3.78) | 0.002 | 4.68 (2.45–8.92) | <0.0001 |
| Mortality under medical management | 24 | 48 | 40 | 1.51 (0.83–2.73) | 0.20 | 1.29 (0.68–2.43) | 0.40 | 3.14 (1.24–7.94) | 0.020 |
| Mortality, ICD implantation, VT ablation under medical management | 24 | 71 | 80 | 2.89 (1.67–5.01) | 0.0002 | 2.41 (1.34–4.32) | 0.003 | 5.80 (2.75–12.23) | <0.0001 |
| Post-operative mortality | 19 | 57 | 75 | 1.12 (0.30–4.12) | 0.90 | 0.96 (0.24–3.84) | 1.00 | 1.79 (0.32–9.98) | 0.50 |
| Post-operative mortality, ICD implantation, VT ablation | 19 | 78 | 100 | 2.59 (0.91–7.36) | 0.07 | 2.36 (0.78–6.96) | 0.10 | 3.69 (0.93–14.74) | 0.06 |

*Versus no/trivial. †Adjusted for age, sex, Charlson index, LVEF, MR grade, MAD.
HR = hazard ratio; ICD = implantable cardioverter-defibrillator; Mod = moderate; other abbreviations as in Tables 1 and 2.

analysis with comprehensive adjustment, the association of mild–moderate arrhythmia with mortality weakened to insignificance ($p = 0.50$), but severe ventricular arrhythmia displayed a powerful association with mortality with risk remaining unaffected by adjustment (adjusted HR: 2.94; 95% CI: 1.36 to 6.36; $p = 0.006$) (Table 3). Association of severe arrhythmia with excess mortality was confirmed by time-dependent analysis from MVP diagnosis (adjusted HR: 3.25; 95% CI: 1.56 to 6.78; $p = 0.002$). Stratified by Holter timing (Supplemental Figures 1 and 2, left panel), severe ventricular arrhythmia association with excess mortality (vs. no/trivial) was powerful under medical management (adjusted HR: 3.14; 95% CI: 1.24 to 7.94; $p = 0.02$) (Table 3) but was weaker post-mitral surgery (adjusted HR: 1.79; 95% CI: 0.32 to 9.98; $p = 0.50$) (Table 3). There was no interaction with Holter timing for arrhythmia severity outcome (all $p \geq 0.06$).

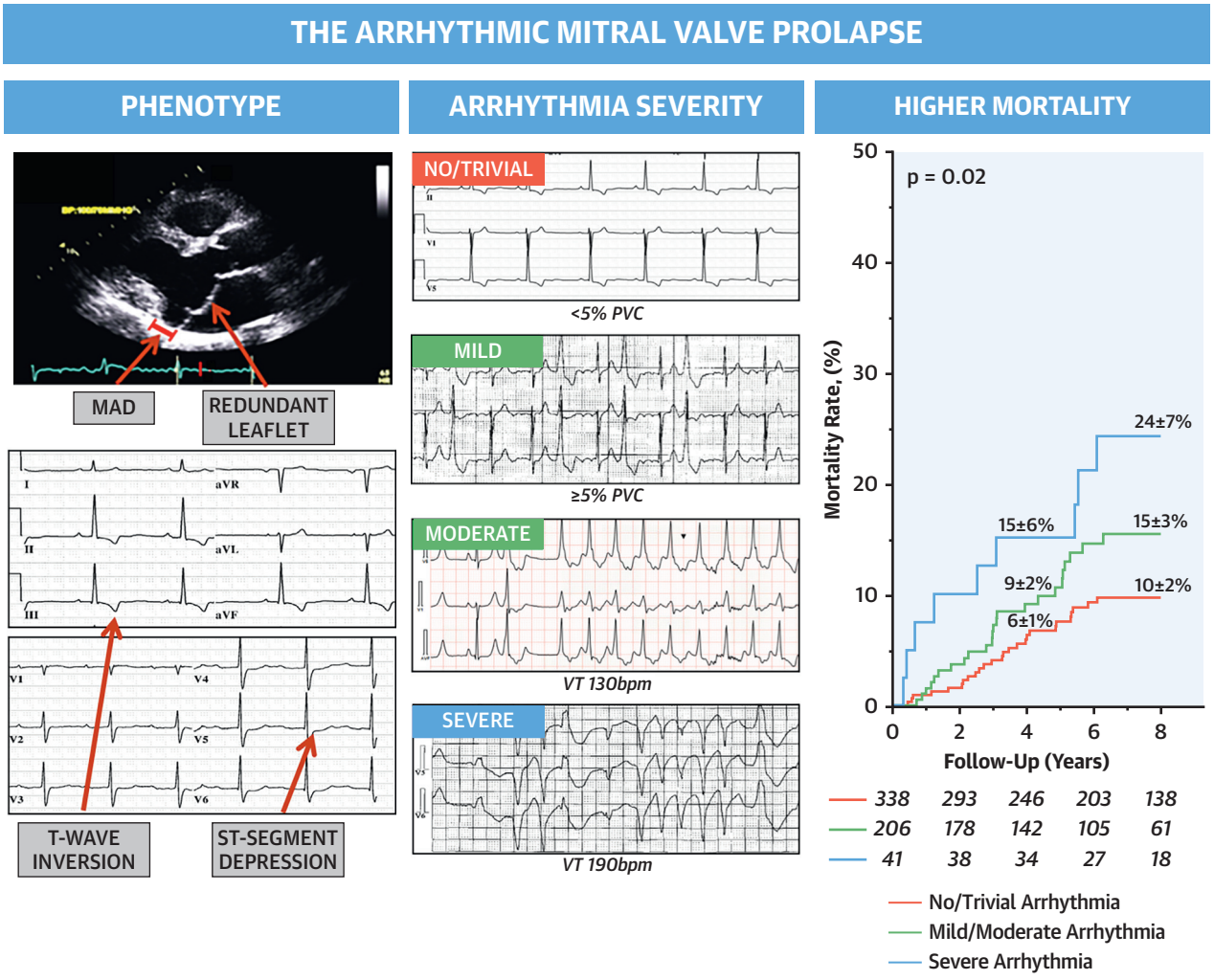
**EVENT-FREE SURVIVAL.** Overall occurrence of ICD and VT ablation was 11 ± 1% at 4 years and 17 ± 2% at 8 years. The 4-year event occurrence was higher for patients without arrhythmia than that for patients with ventricular arrhythmia ($p < 0.0001$). Univariably, the presence of ventricular arrhythmia was strongly associated with event occurrence (univariable HR: 3.11; 95% CI: 1.96 to 4.93; $p < 0.0001$) and remained so after comprehensive adjustment (adjusted HR: 2.66; 95% CI: 1.65 to 4.31; $p < 0.0001$).

The presence of ventricular arrhythmia assessed under medical management remained strongly associated with event occurrence (adjusted HR: 2.89; 95% CI: 1.67 to 5.01; $p = 0.0002$), but the association was weaker when diagnosed after mitral surgery ($p \geq 0.06$). Similarly, no interaction with Holter timing was noted ($p \geq 0.24$).

Ventricular arrhythmia severity was strongly associated with event occurrence with 4- and 8-year rates, respectively, of 6 ± 1% and 10 ± 2% for no arrhythmia, 15 ± 3% and 24 ± 3% for mild–moderate ventricular arrhythmia versus 27 ± 7% and 39 ± 8% for severe ventricular arrhythmia (Figure 2). In univariable analysis, risk of excess mortality, need for an ICD, or VT ablation was considerably higher with HRs of 2.73 (95% CI: 1.67 to 4.44; $p < 0.0001$) for mild–moderate ventricular arrhythmia and 4.95 (95% CI: 2.63 to 9.31; $p < 0.0001$) for severe ventricular arrhythmia versus no arrhythmia. After adjustment, HRs of 2.27 (95% CI: 1.36 to 3.78; $p = 0.002$) for mild–moderate ventricular arrhythmia and 4.68 (95% CI: 2.45 to 8.92; $p < 0.0001$) for severe ventricular arrhythmia versus no arrhythmia remained almost unchanged (Table 3).

Stratified by timing of arrhythmia assessment, the association of more severe ventricular arrhythmia with event occurrence (Supplemental Figure 1, right panel) remained strong under medical management (adjusted HR: 2.41; 95% CI: 1.34 to 4.32; $p = 0.003$), for mild–moderate ventricular arrhythmia (HR: 5.80; 95% CI: 2.75 to 12.23; $p < 0.0001$), for severe ventricular arrhythmia versus no arrhythmia (Table 3), whereas it was much weaker post-operatively (Supplemental Figure 2, right panel, Table 3). However, the interaction with Holter timing was insignificant ($p \geq 0.23$).

**CENTRAL ILLUSTRATION** Arrhythmic Mitral Valve Prolapse Syndrome




Essayagh, B. et al. J Am Coll Cardiol. 2020;76(6):637–49.

**(Left)** Arrhythmic mitral valve prolapse phenotype: **(top)** transthoracic echocardiographic Doppler long-axis systolic view with mitral annulus disjunction (MAD) and leaflet redundancy; **(bottom)** electrocardiographic tracings showing ST-T changes. **(Middle: from top to bottom)** No/trivial, mild, moderate, and severe ventricular arrhythmia. **(Right)** Reduced survival associated with ventricular arrhythmia severity. bpm = beats/min; PVC = premature ventricular complex; VT = ventricular tachycardia.

## DISCUSSION

For the first time, the present study gathered a unique cohort of patients with isolated MVP with comprehensive clinical, echocardiographic, ECG, and rhythmic characterization that was aimed at defining AMVP prevalence, its associated characteristics, and long-term outcome. Of core importance was the ability to stratify the severity of the arrhythmia, which allowed us to examine the impact of each severity grade on outcome, independently of baseline and MR-specific characteristics. By taking advantage of such unique and detailed characterization, we observed a high frequency of ventricular arrhythmias in patients with isolated MVP, but most were mild to moderate; severe arrhythmia seldom affects <1 of 10 patients with MVP. The presence of ventricular arrhythmia was not random and predominated in patients with enlarged-LAs and LVs, although neither MR severity, coronary disease, or LVEF were

independent determinants. The most powerful characteristics associated with severe ventricular arrhythmias were also more MVP specific, with MAD and leaflet redundancy suggesting advanced myxomatous degeneration (an association persistent for arrhythmia detection under medical management and after mitral surgery), as well as suggestive ST-T changes. The most important finding was the outcome significance of ventricular arrhythmia. The robust endpoint of overall survival was strongly and independently linked to severe ventricular arrhythmia, independently of all characteristics (e.g., age, sex, comorbidity) or MVP-specific characteristics (e.g., MR severity, EF, and the presence of MAD) (**Central Illustration**). Event-free survival, including endpoints of ICD and VT ablation, was also markedly affected by the presence of ventricular arrhythmia and severity, particularly when detected under medical management. In light of the results from this large and comprehensive cohort, ventricular arrhythmia, in the context of isolated MVP, particularly when severe, warrants careful clinical attention and well-designed clinical trials to reduce the mortality associated with this serious form of MVP.

**THE CONUNDRUM OF MVP OUTCOME.** MVP is a frequent condition that has baffled investigators in defining its outcome. After the initial clinical description of MVP, the risk of mortality, particularly sudden death, was emphasized (7,9). However, these data were put into doubt when imaging pitfalls of MVP diagnosis were uncovered, and improved criteria were widely accepted (3,4). These changed and improved criteria made most older studies prone to errors and obsolete. After these improved criteria were used, major studies suggested that MVP was a generally benign condition, unless MR of moderate–severe degree or consequent LV dysfunction were noted (2,6). These landmark studies suggested that mortality risk was uniquely consequent to MR (6) and its outcomes, even the risk of sudden death (10). This benign outcome concept of MVP outside of the consequences of MR was shattered by reports that suggested an arrhythmic MVP form that was potentially malignant linked to a high sudden death risk (12,13,35). However, these studies were small and left considerable uncertainty. Therefore, an international collaborative report with the largest cohort of sudden death due to ventricular arrhythmia, without other cause than MVP, raised attention to the possibility of an arrhythmic MVP form independent of MR severity (15). However, cross-sectional studies, although useful in raising awareness to a possible AMVP form, could not affirm whether ventricular arrhythmias were of prognostic significance in patients diagnosed with MVP (17). Therefore, our study, which had the first large cohort of patients with isolated MVP, with presence and severity of ventricular arrhythmias quantified by Holter monitoring, was of critical importance in ascertaining the concept of AMVP. It showed that in patients with MVP, ventricular arrhythmias were frequent but rarely severe. It was essential to define these patients with isolated MVP and severe ventricular arrhythmias because of the link to subsequent mortality established by our large cohort. Hence, for the first time, our study reconciled epidemiological and electrophysiological studies that established the generally benign outcome of isolated MVP as a group and showed that within this large population, a small subset with severe ventricular arrhythmias was at risk of excess mortality. The risk attached to ventricular arrhythmias was also observed in apparently healthy individuals or in those with ischemic heart disease (30). Ventricular arrhythmias are rare in structurally normal hearts but can be associated with increased mortality (30), in proportion to the density and/or complexity of arrhythmias. Similar observation of risk with or without MVP raises questions of whether arrhythmia is linked or independent of MVP and emphasizes the importance of examining whether there is a specific AMVP phenotype that supports the concept of MVP-linked arrhythmias.

**AMVP PHENOTYPE.** Presence of ventricular arrhythmias with MVP was independently and strongly associated with MAD, marked leaflet redundancy, ST-T abnormalities, and secondarily, with enlarged LA or LVESD. Although older age is a factor of the presence of arrhythmia, it is not a hallmark of severe arrhythmias, and no link to coronary artery disease could be uncovered. These clinical, electrocardiographic, and echocardiographic features define a unique MVP subgroup that may follow a course different (not linked to MR severity or LV dysfunction) and more concerning than that of the general MVP population, with worse outcome.

ST-T abnormalities are uncommon without structural heart disease. Prevalence of T-wave inversion in the adult general population is 0.5% to 0.9% (36,37) and is associated with all-cause mortality, cardiac death, and, most importantly, with arrhythmic death among apparently healthy adults. In the MVP context, ST-T changes are frequent and have been touted as linked to SCD (14), but without large cohorts of systematic rhythm evaluation, doubts remain. Hence, our cohort with long-term follow-up

demonstrated that ST-T changes, although frequent, were independently linked to ventricular arrhythmias (38).

MAD mechanisms and their pathophysiological significance remain incompletely delineated but have been touted as contributing to AMVP (24). In our cohort, MAD emerged as one of the strongest independent predictors of ventricular arrhythmia. This observation was particularly important, because, in contrast to previous studies (24), we included patients with and without MAD and with and without arrhythmias. Moreover, arrhythmia risk increased proportionally to MAD length, emphasizing the central role of MAD in the AMVP complex (21). Histopathological and cardiac magnetic resonance imaging examinations established correlation between MAD and LV fibrosis located in papillary muscles and the inferobasal LV wall (12,22). This distribution correlated with common sites of the origin of arrhythmias (12), reinforcing the MAD–arrhythmogenic substrate association (22). However, our study demonstrated that not all MADs were associated with ventricular arrhythmia, which implied that local fibrosis that leads to arrhythmia might be progressive (22,24), and that electrophysiological and morphological characteristics warrant careful monitoring in patients with MVP and marked myxomatous degeneration. A MAD link to ventricular arrhythmia was not isolated but rather associated with advanced myxomatous disease. Consistent with isolated SCD cases (15), our study demonstrated that advanced myxomatous disease with marked redundancy and MAD were key to the AMVP phenotype. Although pathophysiological mechanisms linking ventricular arrhythmia and isolated MVP remained unclear, the present AMVP phenotype might allow a risk stratification scheme.

Isolated reports suggested that female sex was a risk factor for complex arrhythmias (39) and arrhythmic death (12,15), but sex was not independently linked to arrhythmia in our cohort. Similarly, although isolated SCD was easier to diagnose in young individuals and link to MVP (18,24), our cohort did not confirm the youth association of severe AMVP. Hence, our large cohort defined the comprehensive AMVP phenotype, which is crucial in setting the stage for risk stratification and design of clinical trials.

**STUDY STRENGTHS AND LIMITATIONS.** Eligible patients were identified retrospectively but patients' characteristics were acquired prospectively and consecutively. Most Holter and/or echocardiographic variables stored at initial examination were collected without alteration, a strength of our study. Few variables, initially unmeasured, were measured by investigators blinded to outcomes. Holter recordings, indicated by various clinical symptoms and not just palpitations and/or arrhythmias, presented minimal bias in defining arrhythmia prevalence in routine practice, but future systematic Holter monitoring in MVP might be of interest. There was no perfect instrument to detect all arrhythmias over patients' lifetimes, but Holter monitoring remains the standard screening for arrhythmias in routine practice and is superior to standard ECG, whereas invasive electrophysiology or long-term monitoring are not recommended in standard MVP. Determining PVC origin based on surface ECG with 3-leads is only moderately accurate. While definite localization would require invasive electro-anatomical map, our aim was only to differentiate arrhythmia arising from the mitral apparatus or not and in that regard, the 3-lead method can be considered fairly accurate. Although we relied on established algorithms, definite localization would require an invasive electro-anatomical map. However, our aim was only to differentiate arrhythmias arising from the mitral apparatus from the rest. Thus, at this resolution, our method could be considered fairly accurate. Cardiac magnetic resonance imaging, which is useful for scar analysis, is currently not part of routine MVP clinical practice. In view of our results, future prospective AMVP studies should include advanced imaging, including better quantification of MAD by improved spatial and temporal resolution, and arrhythmic evaluation. Sudden death was important but could not be defined in routine practice due to legal limitations for a cause-of-death definition, but overall mortality included these cases and was the most robust outcome measure available. Grading ventricular arrhythmia severity could be disputed, but PVC/VT Holter quantitation is in line with state-of-the-art literature (30–33), and its validity was confirmed by the strong outcome links revealed by our study. Cohorts differed from clinical trials that measured potential benefits of interventions but allowed defining subsets at risk and will be indispensable for future clinical trial design.

## CONCLUSIONS

This large cohort of consecutive patients with isolated MVP, which was comprehensively characterized with 24-h Holter monitoring, as well as clinical and echocardiographic assessment, demonstrated that ventricular arrhythmias are frequent with MVP but rarely severe. AMVP was independently and strongly associated with specific ECG and morphological patterns,

particularly ST-T changes, the presence of MAD, and marked leaflet redundancy, which suggested a specific AMVP phenotype, independent of MR severity. Arrhythmia, particularly severe, was associated with long-term excess mortality and lower event-free survival, particularly under medical management and independent of other characteristics, including MR severity and LVEF. These findings have laid the foundation for novel risk stratification of MVP for the conduct of prospective controlled studies evaluating management of high-risk patients with MVP.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Ventricular arrhythmias occur frequently in patients with MVP but are rarely severe. An arrhythmogenic substrate is associated with a consistent phenotype in a small subset of high-risk patients with MVP, who warrant careful clinical evaluation.

**TRANSLATIONAL OUTLOOK:** Cohort analyses are needed to identify patients with MVP at higher risk of ventricular arrhythmias who could be targeted for controlled studies of management strategies.

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**KEY WORDS** ectopy, mitral valve prolapse, mortality, outcome, ventricular arrhythmia

**APPENDIX** For an expanded Results section and supplemental tables and figures, please see the online version of this paper.