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CLINICAL RESEARCH

Ventricular arrhythmias in arrhythmic mitral valve syndrome—a prospective continuous long-term cardiac monitoring study

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Aims Arrhythmic mitral valve syndrome is linked to life-threatening ventricular arrhythmias. The incidence, morphology and methods for risk stratification are not well known. This prospective study aimed to describe the incidence and the morphology of ventricular arrhythmia and propose risk stratification in patients with arrhythmic mitral valve syndrome.

Methods Arrhythmic mitral valve syndrome patients were monitored for ventricular tachyarrhythmias by implantable loop recorders (ILR) and secondary preventive implantable cardioverter-defibrillators (ICD). Severe ventricular arrhythmias included ventricular fibrillation, appropriate or aborted ICD therapy, sustained ventricular tachycardia and non-sustained ventricular tachycardia with symptoms of hemodynamic instability.

Results During 3.1 years of follow-up, severe ventricular arrhythmia was recorded in seven (12%) of 60 patients implanted with ILR [first event incidence rate 4% per person-year, 95% confidence interval (CI) 2–9] and in four (20%) of 20 patients with ICD (re-event incidence rate 8% per person-year, 95% CI 3–21). In the ILR group, severe ventricular arrhythmia was associated with frequent premature ventricular complexes, more non-sustained ventricular tachycardias, greater left ventricular diameter and greater posterolateral mitral annular disjunction distance (all $P < 0.02$).

Conclusions The yearly incidence of ventricular arrhythmia was high in arrhythmic mitral valve syndrome patients without previous severe arrhythmias using continuous heart rhythm monitoring. The incidence was even higher in patients with secondary preventive ICD. Frequent premature ventricular complexes, non-sustained ventricular tachycardias, greater left ventricular diameter and greater posterolateral mitral annular disjunction distance were predictors of first severe arrhythmic event.

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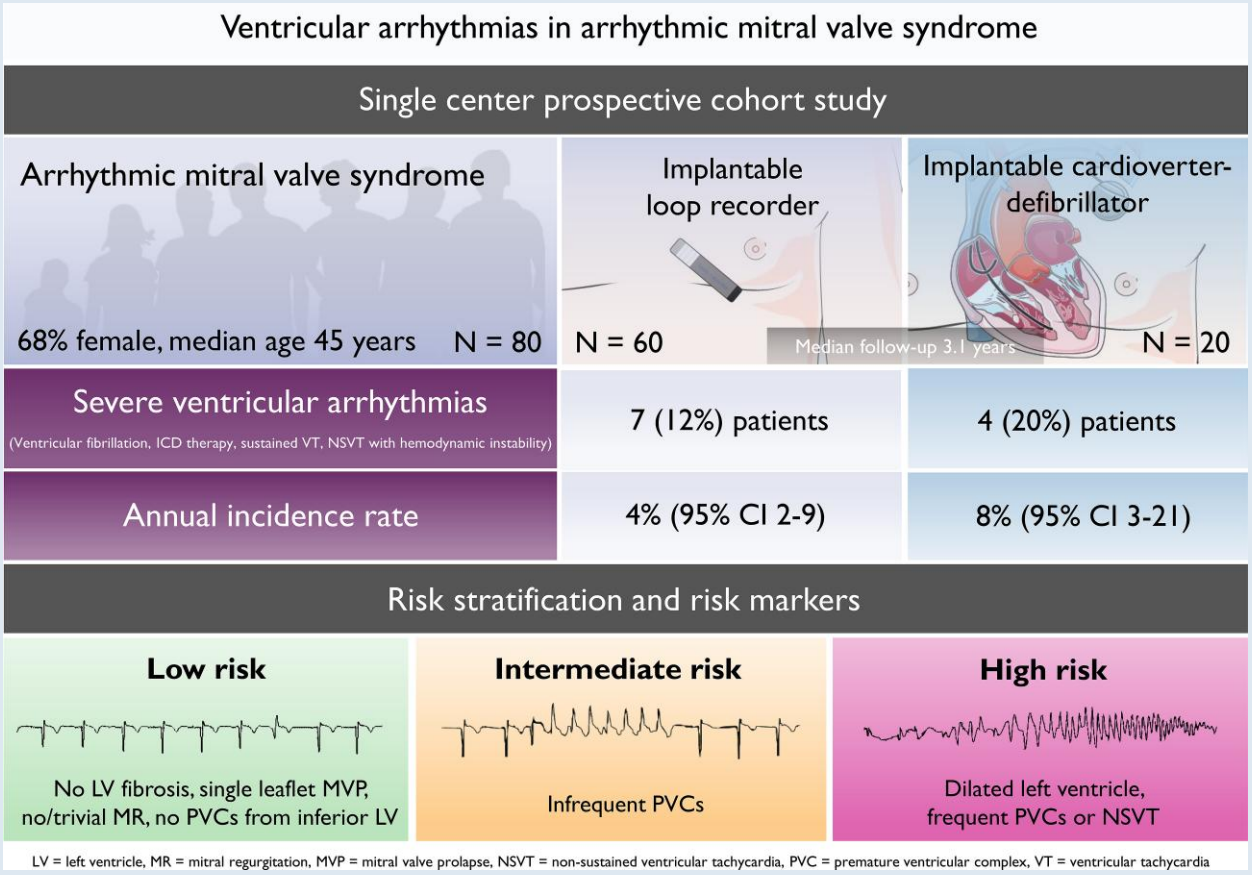
Graphical Abstract



We included 80 patients with arrhythmic mitral valve syndrome followed for 3.1 years; 60 were implanted with a loop recorder (ILR) and 20 had prior implantable cardioverter defibrillator (ICD). Severe ventricular arrhythmia occurred in seven patients (12%) in the ILR-group and four (20%) in the ICD-group. Servier Medical Art. LV = left ventricle, MR = mitral regurgitation, MVP = mitral valve prolapse, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, VT = ventricular tachycardia.

Keywords Mitral valve prolapse • Ventricular tachycardia • Sudden cardiac death • Implantable loop recorder • Cardiomyopathy • Mitral annular disjunction

What's new?

- Patients with arrhythmic mitral valve syndrome are at risk of severe arrhythmic events, and risk stratification could be used to guide proper treatment.
- Patients without prior severe arrhythmic events had a 4% annual incidence of severe ventricular arrhythmic event.
- The annual incidence of severe arrhythmic re-events was 8% among patients with secondary preventive implantable cardioverter-defibrillator.

Introduction

Mitral valve prolapse (MVP) is a common and generally benign condition.[1] The association between MVP and sudden cardiac death was reported several decades ago, with an incidence of 0.2 to 0.4% per year in the general MVP population.[2] However, there is emerging evidence of an arrhythmic phenotype with an unclear incidence of life-threatening arrhythmias.[2] The definition of this syndrome is not clearly established and different terms have been proposed, including arrhythmic MVP.[3,4] Arrhythmic symptoms are common in these patients, and they frequently have multifocal ventricular arrhythmias arising from the outflow tracts, mitral annulus or left ventricular papillary muscles.[4–7] The most widely recognized risk markers are female gender, younger age, bileaflet MVP, T-wave inversions on ECG, left ventricular myocardial fibrosis and mitral annular disjunction (MAD).[7–11] However, current risk markers associated with life-threatening arrhythmias derive from cross-sectional and retrospective studies and lack prospective validation. The incidence of severe ventricular arrhythmias is unknown and clinical decisions on primary prevention implantable cardioverter defibrillator (ICD) remain challenging.

We aimed to describe the incidence of ventricular arrhythmias in patients with arrhythmic mitral valve syndrome. For this, we extended our previous study[9] by using continuous heart rhythm monitoring. We aimed to provide incidence rates and the morphology of ventricular arrhythmias in patients with and without prior severe ventricular arrhythmia. Additionally, we aimed to explore tools for risk stratification, and strategies for follow-up.

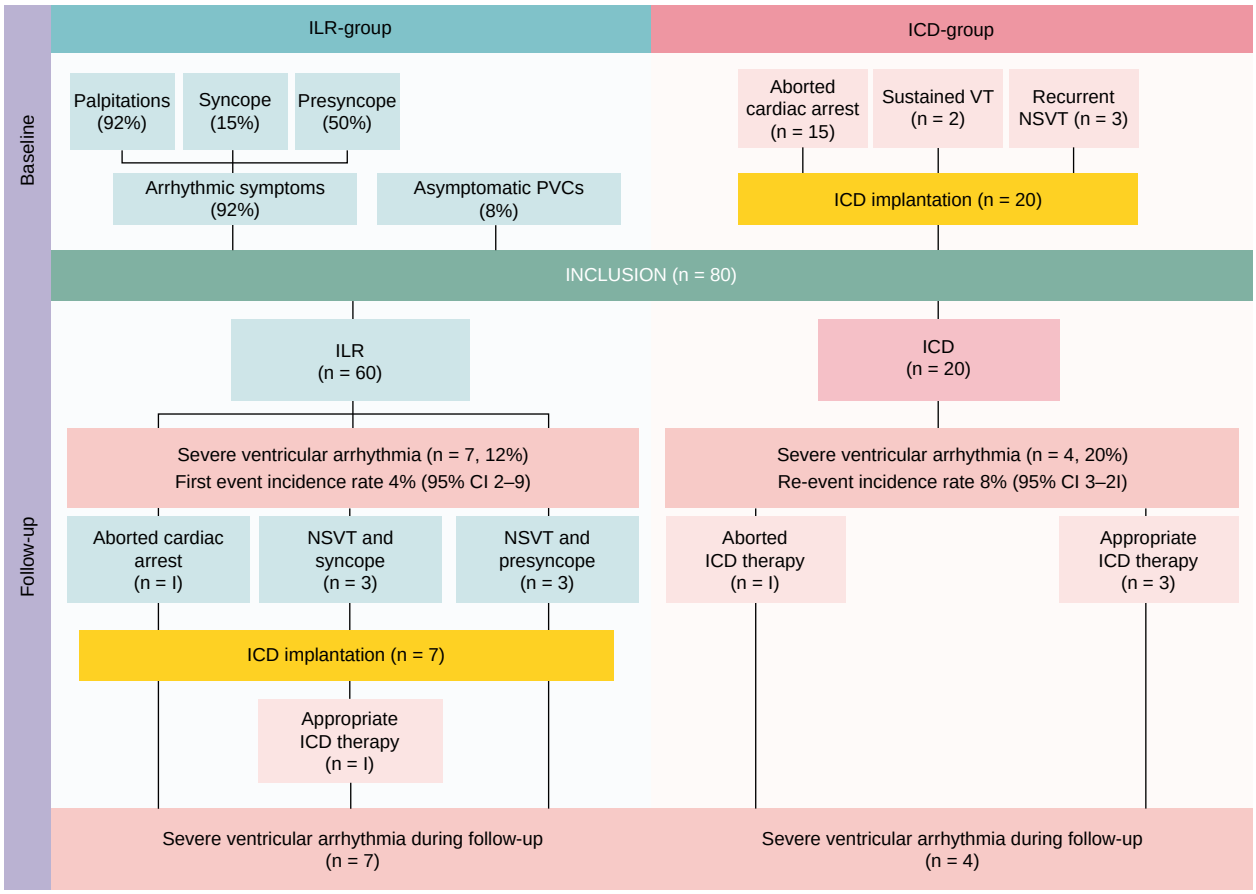


Figure 1 Study flow chart. We included 80 patients with arrhythmic mitral valve syndrome followed for 3.1 years; 60 were ILR and 20 had prior ICD. Severe ventricular arrhythmia occurred in 7 patients (12%) in the ILR-group and 4 (20%) in the ICD-group. One patient with ILR-detected arrhythmia leading to ICD implantation later experienced appropriate ICD shock.

Methods

Study population, study design and recruitment

In this prospective cohort study, we consecutively recruited patients for continuous heart rhythm monitoring following the study procedures from our previously published cohort of MAD patients.[9] In short, we screened patients with possible MAD at two hospitals in Norway, Oslo University Hospital and Drammen Hospital, from August 2015 through August 2020 (see Supplementary material online, *Figure S1*, and Supplementary material online, *Table S1*). If the echocardiographer at these recruiting centers suspected MAD, we invited the patient to a comprehensive study evaluation at Oslo University Hospital, including clinical examination, family history, 12-lead electrocardiogram (ECG), 24 h ECG, stress ECG, transthoracic echocardiography and cardiac magnetic resonance imaging (CMR).

Arrhythmic mitral valve syndrome was defined as MAD and/or MVP with arrhythmic symptoms or documented complex premature ventricular complexes (PVC). Patients with arrhythmic mitral valve syndrome were asked to be part of this prospective follow-up study, if they fulfilled prespecified eligibility criteria. The prespecified eligibility criteria were no prior documented severe ventricular arrhythmia with left ventricular ejection fraction >50% and either inferior T-wave inversions on ECG or one of the following findings on Holter monitoring; non-sustained ventricular tachycardia (NSVT), complex PVCs (multifocal PVCs, or PVCs occurring in bigemini or couplets) or >500 PVCs per 24 h. In those who consented, we implanted a subcutaneous Reveal LINQ (Medtronic, Minneapolis, USA) in the left parasternal area in local anesthesia. Additionally, we included patients with arrhythmic mitral valve syndrome with ICD implanted due to prior severe ventricular arrhythmias. We did not include patients where clinically indicated genetic testing revealed a pathogenic variant, which could explain the phenotype and the arrhythmic event.

End of follow-up was defined as last device interrogation or last transmission of ILR data by remote monitoring. The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics (2015/596/REK nord). All study participants gave written informed consent.

Follow-up by implantable cardiac device

We programmed the ILR to automatically store tachyarrhythmias that persisted for at least five consecutive beats and at heart rates 220 minus patient's age beats/min. We adjusted ILR programming in case of frequent recordings of false events. All patients were on remote monitoring [Carelink™ (Medtronic, Minneapolis, USA)], with possibility for daily alerts if needed. Patients were instructed to activate electrogram recordings manually when experiencing symptoms. We contacted patients with ventricular arrhythmias detected by remote monitoring for assessment of symptoms during the detected arrhythmia, and we evaluated them for ICD implantation. ICD programming was left to the discretion of the treating physicians.

For patients receiving ICD during follow-up, we ended follow-up after the median duration of ILR monitoring (3.1 years) to avoid bias of longer follow-

Table 1 Characteristics of 80 study participants by monitoring device

	All ($n = 80$)	ILR-group ($n = 60$)	ICD-group ($n = 20$)
Female, *n* (%)	56 (68)	44 (73)	11 (55)
Age, years (IQR)	45 (23–59)	49 (37–60)	34 (24–44)
Hypertension, *n* (%)	5 (6)	4 (7)	1 (5)
Atrial fibrillation, *n* (%)	8 (10)	8 (13)	0 (0)
Relevant family history[a], *n* (%)	4 (5)	4 (7)	0 (0)
Antiarrhythmic medication			
Betablockers, *n* (%)	49 (61)	31 (52)	18 (90)
Flecainide, *n* (%)	7 (9)	5 (8)	2 (10)
Amiodarone, *n* (%)	2 (3)	0 (0)	2 (10)
Verapamil, *n* (%)	3 (4)	0 (0)	3 (5)
Arrhythmic symptoms, *n* (%)	66 (83)	55 (92)	11 (55)
Palpitations, *n* (%)	58 (73)	49 (82)	9 (45)
Presyncope, *n* (%)	34 (43)	30 (50)	4 (20)
Syncope, *n* (%)	13 (16)	9 (15)	4 (20)
T-wave inversions, *n* (%)	18 (23)	12 (20)	6 (30)
PVCs, *n* per 24 h (IQR)	280 (41–3525)	232 (33–1329)	2758 (277–6527)
Stress ECG performed, *n* (%)	62 (78)	51 (85)	11 (55)
VA at inclusion, *n* (%)	36 (45)	16 (27)	20 (100)
Aborted cardiac arrest, *n* (%)	15 (19)	0 (0)	15 (75)
Sustained VT, *n* (%)	2 (3)	0 (0)	2 (10)
Non-sustained VT, *n* (%)	19 (24)	16 (27)	3 (15)
Mitral leaflet thickness, mm	3.4 ± 1.2	3.3 ± 1.2	3.5 ± 1.0
Mitral valve prolapse, *n* (%)	58 (73)	47 (78)	12 (60)
Bileaflet MVP, *n* (%)	36 (45)	27 (45)	9 (45)
Myxomatous MVP, *n* (%)	8 (10)	5 (8)	3 (15)
Mitral regurgitation			
None, *n* (%)	24 (30)	21 (35)	3 (15)
Mild, *n* (%)	42 (53)	28 (47)	14 (70)
Moderate, *n* (%)	12 (15)	9 (15)	3 (15)
Severe, *n* (%)	2 (3)	2 (3)	0 (0)
Mitral annular disjunction, *n* (%)	80 (100)	60 (100)	20 (100)
Ejection fraction, %	55 ± 6	56 ± 6	54 ± 6
Arrhythmias during follow-up			
Follow-up duration, years (IQR)	3.1 (2.8–3.3)	3.1 (2.9–3.3)	3.2 (2.0–3.9)
Severe VA, *n* (%)	11 (14)	7 (12)	4 (20)
Severe VA incidence, %/person-years (95% CI)	5 (3–9)	4 (2–9)	8 (3–21)
Non-sustained VT, *n* (%)	37 (46)	24 (40)	13 (65)
Non-sustained VT burden, *n* (IQR)	0 (0–4)	0 (0–2)	3 (0–4)

Values are presented as *n* (%), median (IQR) or mean ± SD. The *P*-values were calculated by means of Student *t*-test, one-way ANOVA, Mann–Whitney U test, chi squared or Fisher exact test as appropriate.

[a]Relevant family history included sudden cardiac death in first-degree relatives ($n = 2$), second-degree relative ($n = 1$) and heart transplantation in first degree relative ($n = 1$). ICD = implantable cardioverter defibrillator, ILR = implantable loop recorder, IQR = interquartile range, MVP = mitral valve prolapse, MR = mitral regurgitation, PM = pacemaker, PVC = premature ventricular contraction, VA = ventricular arrhythmia, VT = ventricular tachycardia.

up in those receiving ICD. We also censored patients undergoing mitral valve surgery or ablation for ventricular arrhythmia at time of the procedure.

Ventricular arrhythmias

We defined NSVT as ≥ 3 consecutive ventricular beats with heart rate > 100 beats/min lasting < 30 s documented by ECG, stress ECG or 24 h ECG at inclusion, or by an implanted cardiac device during follow-up (as per device programming). We defined NSVT burden as the number of NSVTs detected by the cardiac device during follow-up. Severe ventricular arrhythmia was defined as either aborted cardiac arrest, ventricular fibrillation, appropriate or aborted ICD-therapy, sustained ventricular tachycardia (VT) (>100 beats/min lasting >30 s) or NSVT with symptoms of hemodynamic instability (syncope/presyncope).

Table 2 Severe ventricular arrhythmias during follow-up in 60 patients with arrhythmic mitral valve syndrome monitored by implantable loop recorders

	All *n*(= 60)	No severe VA (*n* = 53)	Severe VA (*n* = 7)	*P*-value
Follow-up duration, years	3.1 ± 0.5	3.0 ± 0.5	2.9 ± 0.3	0.44
Female, *n* (%)	44 (73)	38 (72)	6 (86)	0.66
Age, years (IQR)	49 (37–60)	49 (38–60)	46 (27–58)	0.47
Hypertension, *n* (%)	4 (7)	4 (8)	0 (0)	1.00
Atrial fibrillation, *n* (%)	8 (13)	8 (15)	0 (0)	0.58
Antiarrhythmic medication				
Betablockers, *n* (%)	31 (52)	29 (55)	2 (29)	0.25
Flecainide, *n* (%)	5 (8)	5 (9)	0 (0)	1.00
Verapamil, *n* (%)	1 (2)	0 (0)	1 (14)	0.12
Arrhythmic symptoms, *n* (%)	55 (92)	49 (93)	6 (86)	0.48
Palpitations, *n* (%)	49 (82)	44 (83)	5 (71)	0.60
Presyncope, *n* (%)	30 (50)	25 (47)	5 (71)	0.42
Syncope, *n* (%)	9 (15)	7 (13)	2 (29)	0.28
NSVT at inclusion, *n* (%)	16 (27)	10 (19)	6 (86)	0.001
ILR eligibility criterion, ventricular arrhythmia, *n* (%)	45 (75)	38 (72)	7 (100)	0.18
Electrocardiography				
T-wave inversions, *n* (%)	12 (20)	11 (21)	1 (14)	1.00
QTc duration, ms	409 ± 36	410 ± 36	405 ± 38	0.77
PVC per 24 h, *n* (IQR)	231 (33–1329)	154 (25–562)	6682 (612–10 861)	0.01
PVC in bigemini at 24 h ECG, *n* (%)	21 (44)	15 (36)	6 (100)	0.004
NSVT at 24 h ECG, *n* (%)	8 (17)	5 (12)	3 (50)	0.05
NSVT at stress ECG, *n* (%)	3 (6)	0 (0)	3 (50)	0.001
PVC morphology				
Right bundle branch block, *n* (%)				
Superior axis, *n* (%)	28 (48)	22 (43)	6 (86)	0.05
Inferior axis, *n* (%)	12 (21)	10 (20)	2 (29)	0.63
Left bundle branch block, *n* (%)				
Superior axis, *n* (%)	0 (0)	0 (0)	0 (0)	NA
Inferior axis, *n* (%)	11 (19)	10 (20)	1 (14)	1.00
Arrhythmias during follow-up				
NSVT, *n* (%)	24 (40)	17 (32)	7 (100)	0.001
NSVT burden, *n* (IQR)	0 (0–2)	0 (0–1)	4 (4–7)	<0.001
NSVT duration, sec (IQR)	5 (3–7)	5 (2–7)	6 (4–7)	0.28
NSVT highest frequency, bpm	221 ± 31	218 ± 32	229 ± 29	0.45
NSVT shortest cycle length, ms	276 ± 37	280 ± 38	265 ± 32	0.37
Echocardiography				
LV end-diastolic diameter, mm	52 ± 6	51 ± 6	58 ± 6	0.005
LV end-diastolic diameter, mm/m2	29 ± 4	28 ± 4	31 ± 3	0.05
LV ejection fraction, %	56 ± 6	56 ± 6	52 ± 7	0.09
Mitral annular disjunction, *n* (%)	60 (100)	53 (100)	7 (100)	NA
Mitral valve prolapse, *n* (%)	47 (78)	41 (77)	6 (86)	1.00
Bileaflet, *n* (%)	27 (45)	22 (42)	5 (71)	0.27
Mitral regurgitation				0.94
None, *n* (%)	21 (35)	18 (34)	3 (43)	
Mild, *n* (%)	28 (47)	25 (47)	3 (43)	
Moderate, *n* (%)	9 (15)	8 (15)	1 (14)	

Continued

Table 2 *Continued*

	All *n*(= 60)	No severe VA (*n* = 53)	Severe VA (*n* = 7)	*P*-value
Severe, *n* (%)	2 (3)	2 (4)	0 (0)	
Cardiac magnetic resonance (*n* = 53)				
Posterolateral MAD distance, mm (IQR)	4 (0–7)	4 (0–6)	9 (8–12)	0.02
LGE myocardial wall, *n* (%)	7 (15)	5 (12)	2 (40)	0.15
LGE papillary muscle, *n* (%)	11 (23)	9 (21)	2 (40)	0.58
Anterolateral, *n* (%)	5 (11)	4 (10)	1 (20)	0.45
Posteromedial, *n* (%)	10 (22)	8 (20)	2 (40)	0.30
LGE, ml (IQR)	0.3 (0–0.5)	0.2 (0–0.4)	0.3 (0–2.0)	0.86

Values are presented as *n* (%), median (IQR) or mean ± SD. The *P*-values were calculated by means of Student *t*-test, one-way ANOVA, Mann–Whitney U test, chi squared or Fisher exact test as appropriate. IQR = interquartile range, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LV = left ventricular, MAD = mitral annular disjunction, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, RBBB = right bundle branch block, VA = ventricular arrhythmia.

At end of follow-up, we evaluated and reviewed all stored ILR events in the Carelink™ system for ventricular arrhythmias. An expert electrophysiologist re-evaluated and confirmed electrograms considered ventricular arrhythmias and we determined arrhythmia morphology (polymorphic or monomorphic), cycle length and mode of onset. PVC morphology from ECG and stress ECG was categorized in left or right bundle branch block morphology with superior or inferior frontal axis.[12] T-wave inversion was defined as present if seen in ≥ 2 adjacent ECG leads.

Echocardiography and cardiac magnetic resonance

Cardiac volumes and functions were measured according to guidelines.[13,14] Imaging data were analyzed offline [echocardiographic data by EchoPAC v203 (GE Healthcare, Horten, Norway) and CMR data by Sectra Workstation IDS7 v18.1 (Sectra AB, Linköping, Sweden)]. We defined MVP as superior displacement ≥2 mm of any part of the mitral leaflet beyond the mitral annulus on echocardiography using parasternal long-axis view.[13] The mitral valve was defined as myxomatous if leaflet thickness was ≥5 mm. We defined MAD as ≥1 mm disjunction measured in end-systole, from the left atrial wall-valve leaflet junction to the top of the left ventricular wall.[9,15,16] MAD was measured in all locations available for analysis by both echocardiography and CMR, including circumferential extent by CMR.

The CMR study protocol was performed using a 3-T whole-body scanner (Ingenia, Philips Healthcare, Best, the Netherlands). Posterolateral MAD distance was measured on three-chamber view (120 degrees).[9,16] Late gadolinium enhancement (LGE) was reported if present.[9]

Statistical analysis

We presented continuous data as mean with standard deviation or median with interquartile range (IQR), and categorical data as numbers with percentages and compared data with independent Student's *t*-test, one-way analysis of variance (ANOVA), Mann–Whitney U test, chi squared or Fisher exact tests, as appropriate. Univariate cox proportional hazard regression models identified markers of severe ventricular arrhythmias. Significant ($P < 0.05$) variables from the univariate analyses were included in multivariate regression models and were adjusted for age and sex. We tested the multivariate regression models for proportional hazard assumptions to avoid overfitting. We used log base 10 transformation of the PVC burden to meet model linearity assumptions. We reported incidence rates of ventricular arrhythmias using person-years at-risk. We used single threshold regression analysis to explore a cutoff of PVC burden from where the odds of severe ventricular arrhythmia increased the most (Stata/SE v16.1, StataCorp LLC, TX, USA). Two-sided *P* values < 0.05 were considered significant.

Results

Study population for continuous heart rhythm monitoring at baseline

We included 80 patients with arrhythmic mitral valve syndrome (*Figure 1*, *Table 1*) (see Supplementary material online, *Figure S1*). We implanted ILR in 60 (75%) patients meeting ILR eligibility criteria (*Table 2*; see Supplementary material online, *Table S1*). Another 75 patients were screened and either did not meet ILR eligibility criteria or did not consent (see Supplementary material online, *Table S1*). Furthermore, we included 20 (25%) patients with prior ICD due to previous severe ventricular arrhythmia [aborted cardiac arrest (*n* = 15), sustained VT (*n* = 2), and frequent NSVT with syncope/presyncope (*n* = 3)]. CMR was performed in 69 (86%) patients.

Incidence of severe ventricular arrhythmias during follow-up

We followed patients for 3.1 years (IQR, 2.9–3.3), and follow-up was completed in January 2021. None of the patients was lost to follow-up. During follow-up, three patients underwent mitral valve surgery and four patients underwent ablation for ventricular arrhythmia (three in the ILR group and one in the ICD group).

In the ILR group, first severe ventricular arrhythmia occurred in seven (12%) patients (*Figure 1*, left panel), giving an incidence rate of first severe ventricular arrhythmia of 4% per person-year (95% CI 2–9), and 2% per person-year (95% CI 1–6) when including only aborted cardiac arrest, sustained VT and NSVT with syncope as outcome. One patient with ILR-detected NSVT and syncope received ICD and experienced a subsequent appropriate ICD shock for ventricular fibrillation (ILR #1; see Supplementary material online, *Figure S2*).

In the ICD group, severe ventricular arrhythmias occurred in four (20%) patients during follow-up (*Figure 1*, right panel, and see Supplementary material online, *Figure S3*) (two monomorphic and two polymorphic), giving a re-event incidence rate of 8% per person-year (95% CI 3–21).

Ventricular arrhythmias in the implantable loop recorder group

Non-sustained ventricular tachycardias during follow-up

In the ILR-group, NSVT occurred in 24 (40%) unique patients, with an incidence rate of 18% per person-year (95% CI 12–27), of which 11 (45%) did not have NSVT at baseline. We recorded 102 NSVTs in

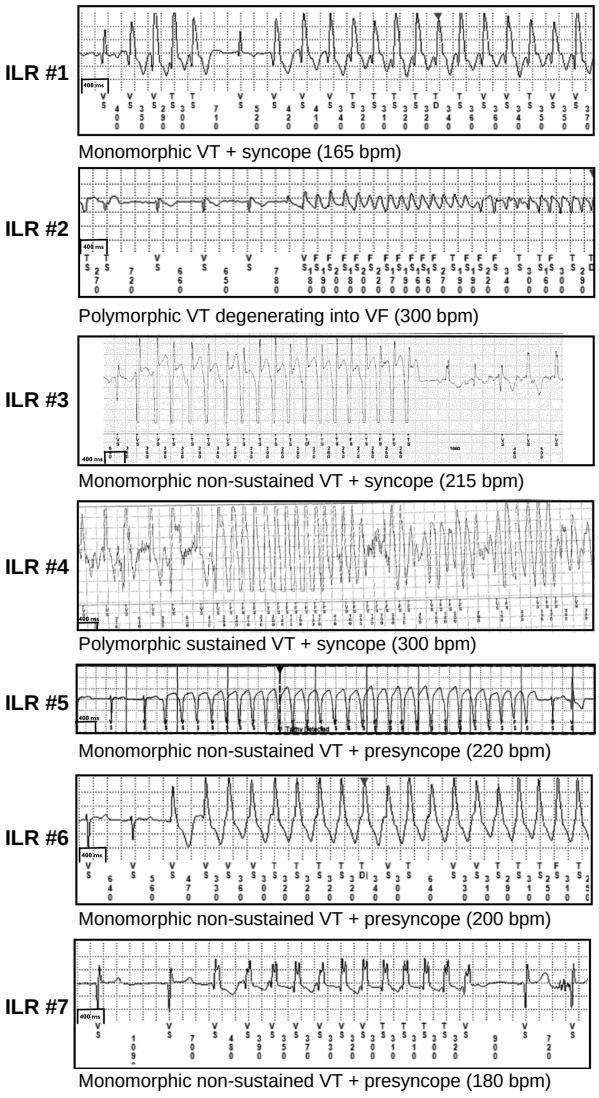


Figure 2 Recordings of the severe ventricular arrhythmias in seven patients with implantable loop recorder at baseline. During follow-up, seven patients had severe ventricular arrhythmias. Patient ILR #1 was implanted with ICD due to frequent NSVTs and syncope at wakeful rest, and experienced appropriate ICD therapy for ventricular fibrillation during mild activity. Patient ILR #2 had polymorphic VT degenerating into VF, which was associated in time with a mitral valve chordal rupture. Patient ILR #3 had monomorphic NSVT causing syncope while standing. Patient ILR #4 had polymorphic sustained VT during exercise with subsequent traumatic head injury. Patient ILR #5 had monomorphic NSVT with presyncope while sitting and carrying a conversation. Patient ILR #6 had monomorphic VT with presyncope while standing. Patient ILR #7 had monomorphic VT with presyncope during wakeful rest.

the 24 patients (ranging from one to 15 episodes in one unique patient), and 88 were due to ILR tachycardia detection and 14 were below the detection zone and, thus, recorded due to symptom activation by the patient. NSVT mean cycle length was 309 ± 93 ms (186 ± 28 bpm) and median duration was eight complexes (IQR, 6–12) [3 s (IQR, 2–4)]. The NSVTs were monomorphic and the arrhythmia initiating PVC coupling intervals varied among the recorded NSVTs [median 530 ms (IQR, 390–650)] and varied within the same patient [maximal variability 310 ms (IQR, 190–480)].

The ILR-detected ventricular arrhythmias led to ICD implantation in ten (17%) of the 60 ILR patients (*Figure 2*; see Supplementary material online, *Figure S2*; see Supplementary material online, *Table S2*). The indications for ICD in these ten patients included severe ventricular arrhythmia ($n = 7$) (*Figure 2*), frequent NSVT despite medical therapy ($n = 1$), and sinus arrest in two patients who received two-chamber ICD due to concomitant recurrent NSVTs (see Supplementary material online, *Figure S4*).

Predictors of occurrence of first severe ventricular arrhythmia in patients monitored by implantable loop recorder

In the ILR group, PVC burden, NSVT burden, left ventricular end-diastolic diameter, and posterolateral MAD distance by CMR were predictors of first severe ventricular arrhythmia in univariate analyses and remained significant when adjusted for age and gender in multivariate analyses (*Table 3*) (all $P < 0.05$).

The odds of severe ventricular arrhythmia increased the most at PVC burden >3525 per 24 h by single threshold regression analysis. Incidence rate for first severe ventricular arrhythmia was 2% (95% CI 0–7) vs. 18% (95% CI 7–49) per person-years in patients with PVC burden below and above 3525 per 24 h, respectively ($P = 0.007$).

LGE, female sex, bileaflet MVP or T-wave inversions were not associated with severe ventricular arrhythmias. There was no difference in occurrence of severe arrhythmias in those fulfilling ILR-eligibility criteria due to ventricular arrhythmias compared to those fulfilling ECG criteria (*Table 2*).

Markers of non-sustained ventricular tachycardia burden

In the ILR-group, markers for greater NSVT burden during follow-up included bileaflet prolapse ($P = 0.04$), LGE in the posteromedial papillary muscles ($P = 0.04$), PVCs with right bundle branch block morphology and superior axis ($P < 0.001$), and moderate/severe mitral regurgitation ($P = 0.03$) (*Figure 3*). Importantly, patients without any of these four markers had no severe ventricular arrhythmias, and had a lower incidence of NSVTs compared to those with ≥1 marker (5% per person-year [95% CI 2 to 15] vs. 29% per person-year [95% CI 19 to 44], $P < 0.001$) (*Figure 3*). We observed no sex differences in the burden of NSVTs ($P = 0.44$), nor differences between patients with and without MVP ($P = 0.78$).

Discussion

The incidence of severe ventricular arrhythmias was high in patients with arrhythmic mitral valve syndrome monitored by ILR or ICD, with a yearly incidence of 4% and 8%, respectively (*Figure 1*). Greater left ventricular dimensions, frequent PVCs, greater ILR-detected NSVT burden during follow-up and greater posterolateral MAD distance identified high-risk patients in the ILR group. The ILR-detected arrhythmias led to ICD implantation in ten of 60 patients. These findings suggest a high diagnostic yield using ILR in patients with arrhythmic mitral valve syndrome.

Incidence, morphology and initiation of ventricular arrhythmias

First severe ventricular arrhythmia occurred in 12% of patients with arrhythmic mitral valve syndrome with no previous severe ventricular arrhythmia, and re-events occurred in 20% of patients with prior severe

Table 3 Univariate and multivariate cox proportional hazard regression for markers of severe ventricular arrhythmias ($n = 7$) in 60 patients with arrhythmic mitral valve syndrome monitored by implantable loop recorders

	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI) adjusted for age and sex	*P*-value
PVC burden per 10-fold increase	1.64 (1.11–2.42)	0.02	1.66 (1.11–2.47)	0.01
PVCs with RBBB superior axis	6.69 (0.81–55.57)	0.08		
NSVT, per 1-increment	1.22 (1.12–1.42)	0.01	1.28 (1.06–1.55)	0.01
Posterolateral MAD distance, per 1 mm-increment	1.27 (1.05–1.55)	0.01	1.43 (1.05–1.96)	0.02
Left ventricular end-diastolic diameter, per 1 mm-increment	1.20 (1.05–1.37)	0.01	1.25 (1.06–1.47)	0.01

Univariate Cox proportional hazard regression was used for markers of severe ventricular arrhythmias during follow-up, and significant parameters were added to separate multivariate regression models to adjust for age and sex. CI = confidence interval, MAD = mitral annular disjunction, NSVT = non-sustained ventricular tachycardia, HR = hazard ratio, PVC = premature ventricular complex, RBBB = right bundle branch block.

ventricular arrhythmia during three years of follow-up. The high rates support the emerging awareness of arrhythmic risk in these patients.

In patients without previous severe ventricular arrhythmia (ILR group), the yearly incidence for first severe arrhythmic event was 4% per person-year. Our incidence was higher than previously reported,[2,17] possibly due to the continuous monitoring used in our study and by our ILR eligibility criteria, which included patients with NSVT, complex PVCs or PVC burden >0.5%.

We included NSVT with presyncope as a severe ventricular arrhythmia, further leading to an increased arrhythmic incidence rate. ESC guidelines state that syncope and presyncope should be evaluated similarly, as they carry the same prognosis.[18] Additionally, patients experiencing NSVTs with presyncope should be evaluated for ICD, and we therefore considered this an important clinical event worthy of prediction. When excluding NSVT with presyncope, the yearly incidence rate was still high at 2%.

Findings by the ILR contributed in decisions on ICD implantation in every sixth ILR monitored patient and the ILR detected arrhythmias that explained clinical symptoms such as syncope/presyncope.

The incidence of NSVTs was high and these NSVTs were monomorphic, mostly of short duration. There were no signs of short-coupled arrhythmic mechanisms. The initiating mechanism should be further investigated.

We also demonstrated an even higher risk of arrhythmic re-events with yearly incidence of 8% in patients with prior ICD, in line with a previous report on MVP patients who survived cardiac arrest by Hourdain *et al.*[6] Both in our study and in the study by Hourdain *et al.*, re-events occurred despite use of antiarrhythmic medication, showing the current lack of efficient non-invasive treatment options.

Risk prediction in patients with arrhythmic mitral valve syndrome

Greater PVC burden and ILR-detected NSVT burden predicted first severe ventricular arrhythmia. A previous study related NSVTs or frequent PVCs on Holter monitoring in patients with MVP to excess long-term mortality.[3] Thus, occurrence of NSVTs should be included as an important risk marker for ICD evaluations (*Figure 4*). Furthermore, having PVCs originating from the inferior left ventricle or papillary muscles was associated with higher NSVT burden in line with previous data,[5] indicating a potential benefit of 12-lead Holter monitoring in these patients.

Neither focal myocardial fibrosis by LGE nor T wave inversions were markers of severe ventricular arrhythmia in our study, contrary to previous studies.[3,8,19] The non-association seen in our study was probably due to our smaller sample size, making our study prone to type II errors. LGE was a marker for ILR-detected NSVT, supporting focal myocardial fibrosis as a substrate for ventricular arrhythmias (*Figure 3*). Importantly, severe arrhythmias occurred also in patients without LGE, emphasizing the need of multiple risk markers. Furthermore, we included T-wave inversion as an ILR eligibility criterion, possibly reducing the predictive power for this parameter within the cohort. Thus, in light of recent studies showing predictive value of LGE and T wave inversions, we believe that these markers should be included in risk stratification.

A greater MAD distance by CMR was associated with severe ventricular arrhythmias, which is in line with other non-prospective studies showing an association with greater MAD distance and complex ventricular arrhythmias.[4,5,7,15] The mechanisms behind the potential association between arrhythmias and greater MAD distance and greater left ventricular diameter need to be explored.

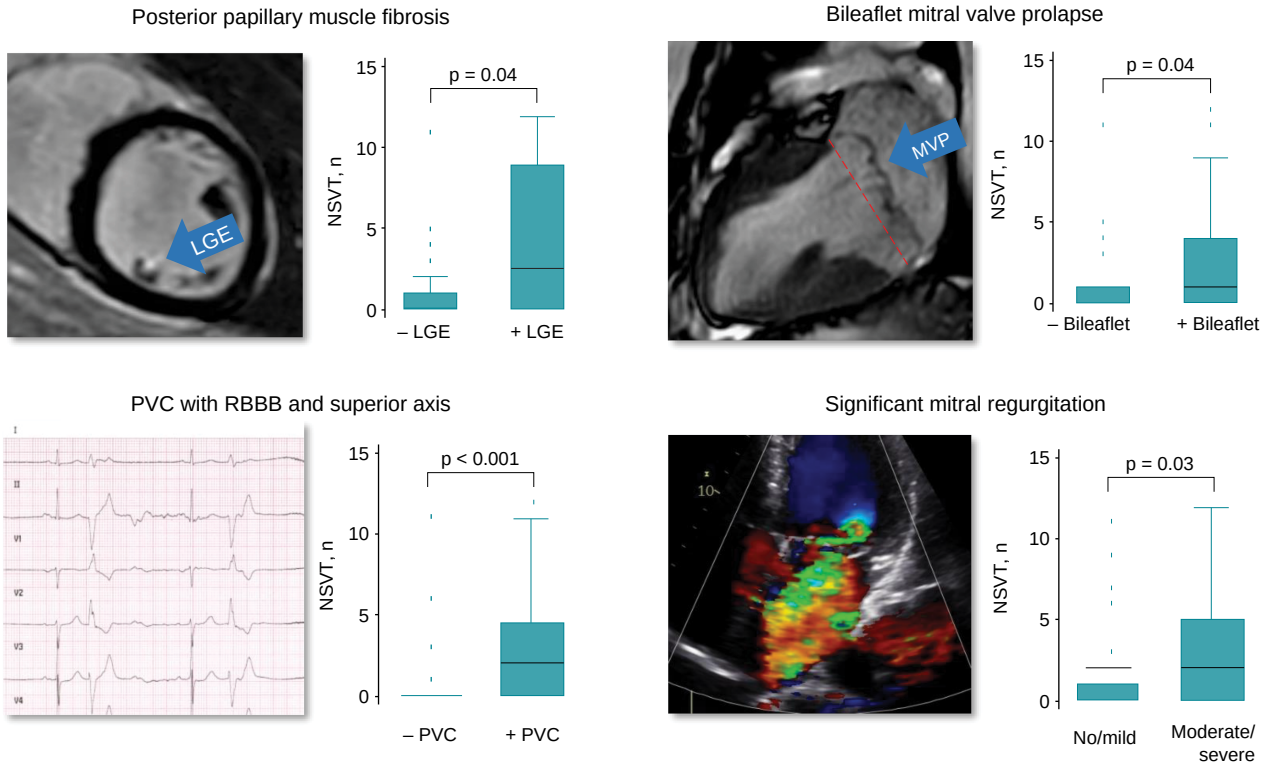
NSVT during stress ECG indicated a value of stress ECG in risk stratification, but was limited by low number of patients.

Use of implantable loop recorder

ILR-detected NSVTs were predictive of severe arrhythmias in our study. Our results suggest that ILR is a useful tool to monitor patients with arrhythmic mitral valve syndrome who do not fulfill indication for primary preventive ICD. During the three years of follow-up, ILR-detected arrhythmias led to ICD implantation in ten patients of which one proved lifesaving with appropriate shock for ventricular fibrillation. Thus, long-term monitoring using ILR led to clinically relevant changes in management and follow-up and we suggest that patients with likely high diagnostic yield should be monitored using ILR (*Figure 4*). However, the prognostic effect of ICD implantation based on ILR-detected arrhythmias remains unknown.

Low risk patients

A low PVC burden showed a reasonable ability to detect patients at lower arrhythmic risk. However, NSVTs occurred also in patients with infrequent PVCs, suggesting that a low PVC count was not sufficient to define a low risk patient. Patients without any of the four NSVT risk markers (LGE, bileaflet MVP, moderate/severe mitral regurgitation and left-sided origin of PVCs) reassuringly seemed at low arrhythmic risk with only 5% yearly incidence of NSVT and with no severe arrhythmic events (*Figures 3* and *4*). These four markers have been associated with unfavorable outcome in MVP patients in other studies,[3,19] and the lack of all of these parameters could reassure low arrhythmic risk.



	NSVT markers		
	0 markers	≥ I markers	p-value
Severe VA incidence rate, %/person-years [95% CI]	0% [0–0]	7% [3–14]	0.04
NSVT incidence rate, %/person-years [95% CI]	5% [2–15]	29% [19–44]	<0.001

Figure 3 Markers of greater NSVT burden detected by implantable loop recorder in 60 patients with arrhythmic mitral valve syndrome. NSVT occurred in 24 (40%) patients during 3.2 years (interquartile range 3.0–3.5). NSVT burden was greater in patients with posteromedial papillary muscle LGE, bileaflet prolapse, moderate/severe mitral regurgitation or premature ventricular complexes with right bundle branch block and superior axis. Absence of any of these markers was related to low arrhythmic risk. RBBB = right bundle branch block, VA = ventricular arrhythmia.

Definition and suggested follow-up in arrhythmic mitral valve syndrome

We propose that the diagnosis of arrhythmic mitral valve syndrome should be defined as MVP and/or MAD in presence of documented PVCs or severe arrhythmic events not explained by other etiologies. These patients should undergo a careful risk stratification. Holter monitoring is important for PVC quantification and for detection of NSVT, as frequent PVCs and NSVTs related to increased arrhythmic risk. Longer and repeated Holter monitoring may reduce errors due to arrhythmia day-to-day variations, and 12-lead Holter monitoring may increase precision by analyses of arrhythmia origin.

Additionally, CMR carries prognostic information with the presence of MAD, posterolateral MAD distance and focal myocardial fibrosis by LGE. Patients without LGE, bileaflet MVP, significant mitral regurgitation and without PVCs originating from the inferior left ventricle may be considered at low arrhythmic risk (*Figure 4*). In contrast, frequent PVCs, occurrence of NSVT, greater posterolateral MAD or dilated left ventricle indicate high arrhythmic risk, and we propose that these patients may be considered for either long-term monitoring with ILR or primary preventive ICD. NSVTs causing symptoms of presyncope/syncope would indicate highest risk and possibly favor primary preventive ICD as also suggested by guidelines[20] (*Figure 4*). We lack data and clinical trials on selection of patients with arrhythmic mitral valve syndrome for primary preventive ICD implantation, and management of these patients vary between centers and countries. The results from our study suggest that high- or intermediate-risk patients might be further risk stratified using ILR (*Figure 4*). Importantly, long-term cardiac monitoring does not replace primary prophylactic ICD implantation in very high-risk patients.

Study limitations

Inherent to the study design using implantable devices, we had a small sample size and provided a limited number of severe ventricular arrhythmias affecting the statistical robustness for exploring risk markers. Larger and independent cohorts of arrhythmic mitral valve syndrome patients should validate our findings.

Our cohort consisted of a selected and symptomatic group of patients that had a clinical indication for referral to a cardiologist, and

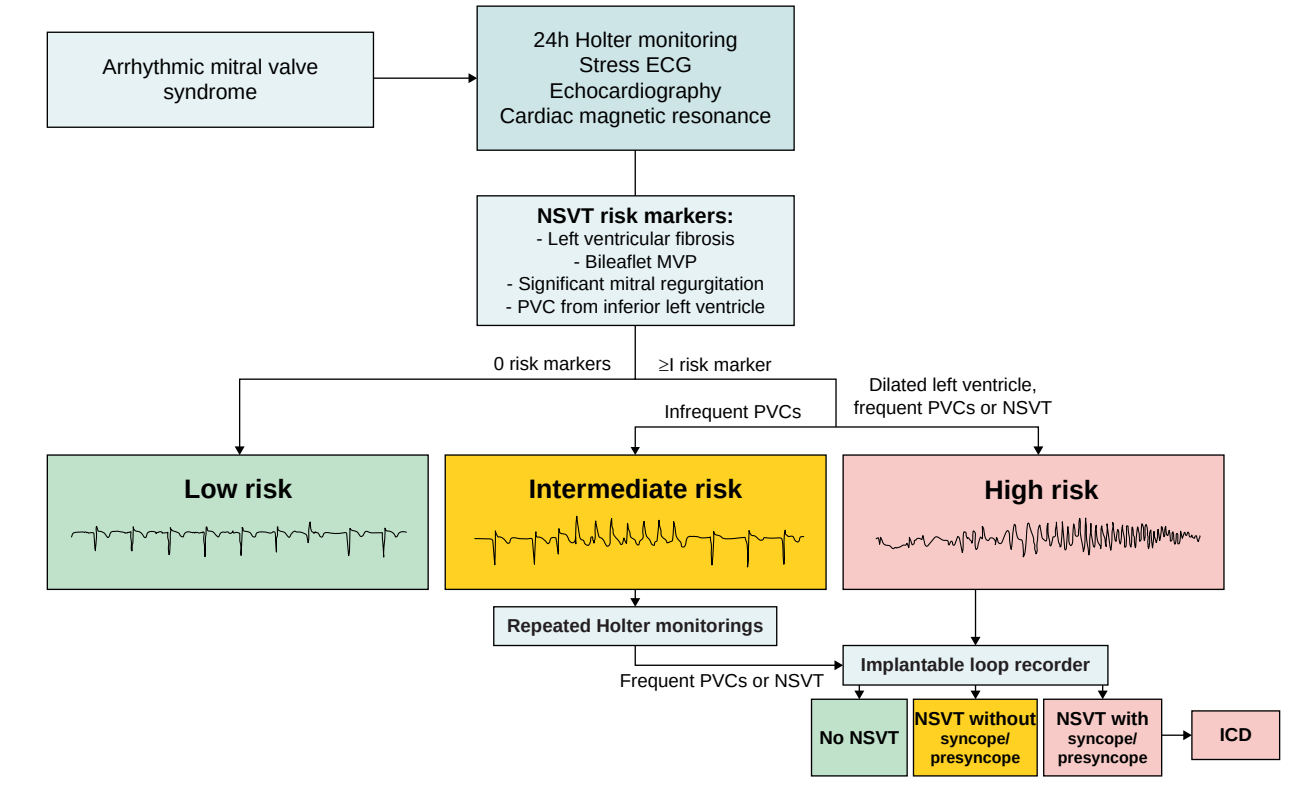


Figure 4 Suggested follow-up in patients with arrhythmic mitral valve syndrome. Patients with arrhythmic mitral valve syndrome should undergo 24 h Holter monitoring, stress ECG, echocardiography and cardiac magnetic resonance for risk stratification. Patients without any of the NSVT risk markers reassuringly seemed at low arrhythmic risk. The presence of NSVT risk markers and dilated left ventricle, frequent PVCs or NSVT could help guide selection of patients for prolonged arrhythmia monitoring by implantable loop recorder.

consequently, the results of our study do not translate to the general MVP population nor to asymptomatic individuals with incidental finding of MVP/MAD. This selective inclusion also affects the external validity of our results. The incidence of ventricular arrhythmias in the general MVP cohort is expected to be considerably lower, as shown in a recent paper by Essayagh *et al.*[17]

The MAD cut-off was arbitrary chosen to define presence of MAD, and confirmed by CMR.

The cardiac devices did not record asymptomatic ventricular arrhythmias with rate or duration below the programmed detection zones, and the overall incidence of ventricular arrhythmias might be underestimated. The discrepancy between VT heart rate cutoffs due to programming differences between ICD and ILR, as well as between various ICDs, is a technical limitation difficult to avoid and inherent to cardiac devices. The single electrogram recordings made it impossible to distinguish arrhythmias originating outside of the mitral valve apparatus in outcome analyses.

We did not use 12-lead Holter monitoring in our study, and the origin of PVCs seen on Holter monitoring could not be determined. Future studies should include 12-lead Holter monitoring with longer duration.

The eligibility criteria used in our study were not meant for clinically selecting patients for ILR monitoring, and should not be used as such in the lack of validation. Additionally, our study was not designed to evaluate the clinical value of systematic ILR implantation in patients with arrhythmic mitral valve syndrome, nor the effect of primary preventive ICD implantation. Whether long-term cardiac monitoring leads to improved prognosis in these patients is still unknown.

The assessment of MVP in presence of MAD is not clearly defined. Future guidelines should address this challenge. We did not assess leaflet redundancy nor curling, which have been associated with ventricular arrhythmias in previous studies.[3]

Conclusion

This is the first prospective follow-up study with extensive continuous cardiac rhythm monitoring in patients with arrhythmic mitral valve syndrome. Using ILR and ICD as monitors, yearly incidence rate of first severe ventricular arrhythmia was 4%, and was 8% for re-events in a selected arrhythmic population. Frequent PVCs, more NSVTs during follow-up, as well as greater left ventricular diameter and greater posterolateral MAD distance, predicted first severe ventricular arrhythmia.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: None declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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