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CLINICAL RESEARCH

Predictive value of ambulatory ECG monitoring for malignant arrhythmic events in genetic dilated cardiomyopathy

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Aims Evaluate the prognostic significance of arrhythmias and conduction disorders on ambulatory ECG in recently diagnosed genetic vs. non-genetic dilated cardiomyopathy (DCM).

Objective To compare the prevalence of abnormalities on ambulatory ECG monitoring between genetic and non-genetic DCM patients and evaluate the predictive value for malignant ventricular adverse events (MVAEs).

Methods and results Clinical and ambulatory ECG data were collected from 354 genotyped DCM probands, with a median follow-up of 8 years (IQR: 5–9 years). The malignant ventricular adverse event was defined as ventricular fibrillation, sustained ventricular tachycardia, anti-tachy pacing, appropriate device therapy, or sudden cardiac death. *C*-statistics assessed the predictive performance of the regression models. In total, 123 (35%) patients carried a (likely) pathogenic variant. Abnormalities on ambulatory ECG were more frequent in genetic DCM patients (80%) compared to non-genetic DCM (67%; $P = 0.013$). Permanent atrial fibrillation (perAF), paroxysmal supraventricular tachycardia (parox-SVT), and non-sustained ventricular tachycardia (NSVT) were more frequent in genetic DCM patients ($P = 0.041$, <0.001, and <0.001). Structural cardiac parameters showed minimal group differences. Using Cox proportional hazard analyses to predict MVAE, ambulatory ECG variables (perAF, AV-block, NSVT, >500 premature ventricular complexes (PVCs)/24 h) had an area under the curve (AUC) of 0.768 in genetic and 0.628 in non-genetic DCM patients ($P = 0.044$). The premature ventricular complex burden was only predictive for MVAE in genetic DCM. Adding clinical variables provided little incremental predictive value for genetic vs. non-genetic DCM (AUC Δ+0.004 vs. Δ+0.150, respectively).

Conclusion Ambulatory ECG monitoring abnormalities are prevalent in genetic DCM patients. In contrast to non-genetic DCM patients, ambulatory ECG parameters have an important predictive value to determine the risk of MVAE in genetic DCM patients.

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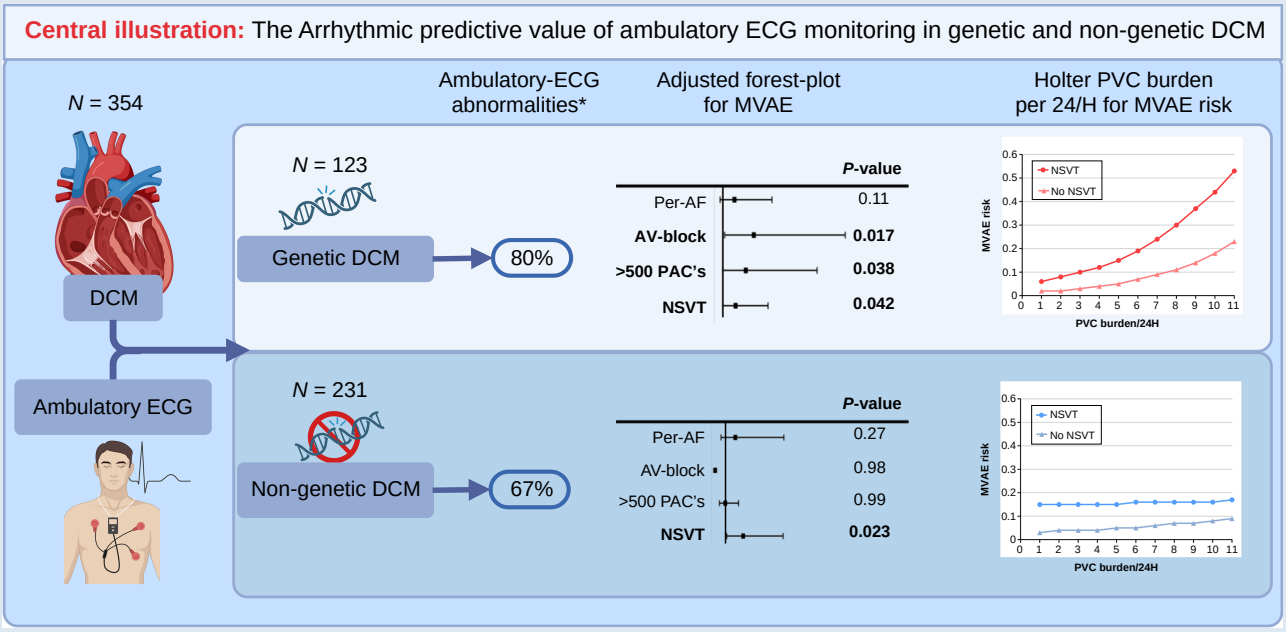
Graphical Abstract



The arrhythmic predictive value of ambulatory ECG monitoring in genetic and non-genetic DCM. The predictive value of ambulatory ECG monitoring parameters for the occurrence of malignant ventricular adverse events for both genetic and non-genetic DCM. * ambulatory-ECG abnormalities were defined as the presence of persistent or permanent atrial fibrillation (perAF), atrioventricular block (any degree), left bundle branch block, right bundle branch block, sinus arrhythmia, >500 PAC/24 h, paroxysmal supraventricular tachycardia (parox-SVT), >500 PVC/24 h or the presence of NSVT, which was defined as ≥3 consecutive ventricular beats at ≥100 bpm lasting <30 s. Abbreviations: AV-block indicates atrioventricular block; DCM, dilated cardiomyopathy; MVAE, malignant ventricular adverse event; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial complex; per-AF, persistent/permanent atrial fibrillation.

Keywords Dilated cardiomyopathy • Ambulatory ECG monitoring • Genetic-DCM • Malignant ventricular arrhythmias

What's new?

Competency in medical knowledge

- Genetic dilated cardiomyopathy (DCM) shows a high prevalence of conduction and rhythm abnormalities at diagnosis.
- Baseline ambulatory ECG monitoring provides significant predictive value for major ventricular arrhythmic events in patients with genetic DCM.
- These findings support the routine use of ambulatory ECG monitoring for early risk stratification in genetic DCM, independent of structural cardiac differences.

Translational outlook

- Prospective studies are needed to validate the prognostic role of ambulatory ECG monitoring in genetic DCM and assess its impact on clinical decision-making.
- Genotype-specific studies, adequately powered for subgroup analyses, are required to determine the predictive and clinical utility of ambulatory ECG monitoring across different genetic variants.

Introduction

Dilated cardiomyopathy (DCM) is characterized by the presence of left ventricular (LV) dilatation and systolic dysfunction unexplained solely by abnormal loading conditions or coronary artery disease.[1] Dilated cardiomyopathy can result from genetic variants, non-genetic triggers, or a combination of both.[2] Pathogenic and likely pathogenic (P/LP) genetic variants are detected in up to 35% of patients with DCM and are generally associated with a worse prognosis.[3–5] Arrhythmias, but also conduction disorders in some genotypes, are prevalent in genetic DCM and mediate the increased risk of adverse outcomes.[5] Electrical disturbances often precede systolic dysfunction in patients with P/LP variants,[6] highlighting the need to screen for arrhythmias in patients with DCM.[1]

Most studies assess the prevalence of arrhythmias and/or conduction disorders based on previous history, ECG or ambulatory ECG monitoring at a single cross-sectional moment during the disease. Moreover, more detailed ambulatory ECG monitoring parameters, such as the frequency of non-sustained ventricular tachycardia (NSVT) and supraventricular tachycardia (SVT), and premature ventricular and atrial contractions (PVC and PAC) burden, are often not investigated. Data on the prevalence of these electrical abnormalities detected at baseline in genetic and non-genetic patients are scarce, and their predictive value for malignant ventricular arrhythmic events (MVAE) in DCM remains unclear.

In this study, we analysed ambulatory ECG data collected at baseline of proband DCM patients in the presence or absence of a P/LP variant, assessing the prevalence of arrhythmias and conduction disorders. Additionally, we investigated the prognostic relevance of the individual ambulatory ECG parameters to predict MVAE in addition to frequently used clinical predictors.

Methods

Study design and population

Patients with DCM were consecutively enrolled in the Maastricht Multicenter Cardiology Monitoring Platform (mCMP-registry) between 2004 and 2024.[7] The inclusion criteria for the DCM registry are adult patients with a left ventricular ejection fraction (LVEF) below 50% and/or a LF end-diastolic diameter or volume above 2 z-scores measured by baseline echocardiography, who provided informed consent. These patients are collectively referred to as DCM in this manuscript. Patients with significant coronary artery disease or abnormal loading conditions (e.g. severe valvular disease) were excluded from the registry.

For the current study, we selected patients with available ambulatory ECG monitoring at baseline (i.e. within 12 months after the diagnosis of DCM). Patients with cardioverter-defibrillators (ICD) or pacemakers (PM) and a paced rhythm were excluded. All patients underwent a physical examination, blood sampling, 12-lead ECG, a complete echocardiographic and Doppler evaluation, and coronary angiography at baseline. All patients received genetic counselling and testing using a gene panel, including at least the 12 DCM-associated genes that are curated as having definitive or strong evidence by the ClinGen DCM gene curation expert panel (see Supplementary material online, *Table S1*). The study was performed according to the Declaration of Helsinki and was approved by the local Medical Ethics Committee (21-017).

Ambulatory ECG monitoring

All patients underwent ambulatory ECG monitoring ranging from 24 to 72 h within 12 months of diagnosis, which was defined as baseline. All ECG data were evaluated by a qualified cardiac electrophysiologist. Rhythm, conduction, supraventricular, and ventricular parameters were collected and analysed. All parameters were normalized to 24 h if the duration was longer than 24 h. Abnormalities were defined as the presence of persistent or permanent atrial fibrillation (perAF), atrioventricular block (any degree), left bundle branch block, right bundle branch block, sinus arrhythmia, >500 PAC/24 h, paroxysmal supraventricular tachycardia (parox-SVT), >500 PVC/24 h or the presence of NSVT, which was defined as ≥3 consecutive ventricular beats at ≥100 bpm lasting <30 s, as described previously.[5]

Follow-up

Information about the occurrence of adverse events at follow-up was retrieved from the medical records, municipal population register, and/or telephone contact with general practitioners. All adverse events were systematically reviewed by an adjudication board to confirm their validity. The median follow-up time was 8 years (interquartile range of 5–9 years). The primary endpoint was MVAE, which was a composite endpoint of ventricular fibrillation, sustained ventricular tachycardia, sudden cardiac death, antitachy pacing, and appropriate device therapy.

Statistical analysis

Variables are displayed as mean ± SD, median [IQR], or frequencies (percentage) as appropriate. A normal distribution of continuous variables was determined using histograms and Q-Q plots. Groups were compared using Pearson χ^2 tests (or the Fisher exact test where necessary) for categorical variables and independent sample Student's *t*-tests for normally distributed or Mann–Whitney *U* tests for non-normally distributed continuous variables. Kaplan–Meier survival curves were estimated with MVAE as the independent variable, and differences between survival distributions were determined using the log-rank test. Uni- and multivariable Cox proportional hazard regression analyses were performed to determine the HR and 95% CI for each parameter. To determine the goodness of fit for the final model, concordance statistic (*C*-statistics) were performed. To see if known clinical covariates [age, sex, left atrial volume index (LAVi), LVEF, and late gadolinium enhancement] influence the predictive value of the final model, a model with and without clinical covariates was made. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA) and R version 2024.12.1 (R Foundation for Statistical Computing, Vienna, Austria) (figures were produced using the packages ggplot2, survival, survminer) software. A *P* value <0.05 was considered statistically significant.

Results

Cohort demographics

In total, 354 patients with DCM were included, with a mean age of 54 ± 12 years, and 223 (63%) were male. The median baseline LVEF was 37% (interquartile range: 27–46) with an indexed LF end-diastolic diameter of 30 ± 5 mm. In total, 123 (35%) patients had a P/LP variant. Truncating variants in *TTN* (TTNtv) were the most prevalent and were detected in 58 (16%) patients, followed by variants in *LMNA* (5%, $n = 18$), *MYH7* (3%, $n = 11$), and *FLNC* (2%, $n = 7$).

Ambulatory ECG analysis

Overall, 98 patients with genetic DCM (80%) vs. 155 patients with non-genetic DCM (67%) had at least one abnormality [perAF, atrioventricular block (any degree), LBBB, RBBB, sinus arrhythmia, > 500 PAC or PVC/24 h, parox-SVT, or NSVT] during ECG monitoring ($P = 0.013$; *Table 1*). Patients with DCM due to a P/LP variant exhibited a higher frequency of perAF, parox-SVT, and NSVT ($P = 0041$, <0.001, and <0.001, respectively; *Table 1*), which was independent of age of diagnosis, sex, or body mass index (*Table 2*). Conversely, parox-SVT and NSVT on ambulatory ECG monitoring had good predictive value for the presence of a P/LP variant in a patient with DCM (area under the curve, AUC: 0.681 [0.618–0.744]). Especially the presence of a parox-SVT had high predictive value (OR 4.74, 2.52–8.93, Wald 23.206, $P < 0.001$).

Pathogenic variants were identified in 13 different genes, varying from one affected patient (e.g. *BAG3*) to 58 patients (TTNtv). To gain insight into the differences between specific genotypes, we analysed the data from the four most prevalent genotypes (TTNtv, $n = 58$; *LMNA*, $n = 18$; *MYH7*, $n = 11$; and *FLNC*, $n = 7$; Supplementary material online, *Table S2*). Patients with a *LMNA* variant had a notably high prevalence of atrial and ventricular abnormalities such as perAF, parox-SVTs, NSVTs, and PVCs, while patients with a *FLNC* variant had mainly ventricular disturbances such as NSVTs and PVCs (see Supplementary material online, *Table S2*). *Figure 1* shows examples of ambulatory ECG abnormalities for TTNtv, *LMNA*, and *FLNC*, respectively. Abnormalities at ambulatory ECG monitoring were less prevalent in patients with a *MYH7* variant.

Structural parameters

Despite the significant differences in the prevalence of arrhythmias and conduction disorders on ambulatory ECG monitoring, there were only minor differences in the structural parameters as measured with baseline echocardiography and cardiac magnetic resonance: only LAVi was significantly increased in patients with genetic DCM ($P = 0.009$; *Table 2*). The LAVi was significantly associated with the prevalence of AF (Pearson's $r = 0.33$, $P < 0.001$).

Prognostic value of ambulatory ECG monitoring

In total, 53 patients (15%) had a MVAE after a median follow-up time of 7 years (interquartile range of 4.3–11 years), of which 27 patients had a P/LP variant (see Supplementary material online, *Table S3*). Overall, a P/LP variant is associated with the occurrence of a MVAE (HR 1.83, 1.06–3.14; $P = 0.027$; *Figure 2*).

We performed Cox regression in patients with and without a P/LP variant separately to determine the role of ambulatory ECG monitoring in these patient groups individually. As an exploratory analysis, we performed univariable analysis on the two most prevalent genotypes (TTNtv and *LMNA*) to gain insight into the genotype-specific prognostic value (see Supplementary material online, *Table S4*).

Table 1 Overview of atrial and ventricular measures of the ambulatory ECG monitoring

	Genetic DCM ($n = 123$)	Non-genetic DCM ($n = 231$)	*P*-value
Any abnormality, *n* (%)	98 (80)	155 (67)	**0.013**
Heart rhythm			
Persistent/permanent Atrial fibrillation, *n* (%)	20 (16)	18 (8)	**0.014**
Mean heart rate, bpm	75 ± 12	74 ± 11	0.64
Minimum heart rate, bpm	51 ± 10	49 ± 8	0.09
Maximum heart rate, bpm	124 ± 24	126 ± 23	0.62
Conduction disorders			
Atrioventricular block, *n* (%)	7 (6)	13 (5)	0.98
First degree block, *n* (%)	6 (5)	12 (5)	0.89
Second degree block, *n* (%)	1 (1)	1 (1)	0.99
Left bundle branch block, *n* (%)	9 (7)	20 (9)	0.66
Right bundle branch block, *n* (%)	2 (2)	3 (1)	0.99
Sinus arrhythmia, *n* (%)	3 (2)	0 (0)	**0.041**
Supraventricular parameters			
Premature atrial contraction/24-h, *n*	53 [10–347]	27 [4–159]	**0.028**
>500 PAC/24-h, *n* (%)	20 (16)	31 (13)	0.21
Paroxysmal SVT, *n* (%)	34 (28)	19 (8)	**<0.001**
Number of SVT/24-h, *n*	2 [1–5]	3 [1–4]	0.56
Longest SVT, QRS complexes	9 [6–16]	7 [4–52]	0.43
Fastest SVT, bpm	121 [108–136]	123 [103–151]	0.98
Ventricular parameters			
Premature ventricular contraction/24-h, *n*	667 [50–4102]	366 [16–2478]	0.07
>500 PVC/24-h, *n* (%)	68 (55)	109 (47)	0.08
Non-sustained ventricular tachycardia, *n* (%)	46 (37)	39 (17)	**<0.001**
Number of NSVT/24-h, *n*	2 [1–3]	1 [1–1]	**0.014**
Longest NSVT, QRS complexes	8 [5–10]	0 [0–6]	0.73
Fastest NSVT, bpm	145 [116–163]	121 [112–154]	0.24

Values are displayed as number (percentage), mean ± standard deviation or median [interquartile range] as appropriate.
bpm indicates beats per minute; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contraction; PVC, premature ventricular contraction; SVT, supraventricular tachycardia.

Overall, an electrical abnormality was predictive for a MVAE in patients with a genetic aetiology (HR 9.02 [1.22–66.7], $P = 0.03$), but not in patients without a P/LP variant (HR 1.84 [0.69–4.93], $P = 0.23$; *Table 3*). Seven variables were significantly predictive in patients with genetic DCM (perAF, maximum heart rate, AV-block, >500 PVC/24 h, NSVT, number of NSVT/24 h, and number of QRS complexes of the longest NSVT) vs. only two parameters in patients with non-genetic DCM (NSVT and number of NSVT/24 h; *Table 3*). We also performed the analysis with ATP excluded from the MVAE as a sensitivity analysis (see Supplementary material online, *Tables S5–S6*), which provided comparable results.

Combining the ECG variables that showed predictive value (perAF, AV-block, NSVT, >500 PVC/24 h) provided an AUC of 0.768 and 0.628 for the prediction of MVAE in genetic and non-genetic DCM patients, respectively ($P = 0.044$; *Table 4*). When combining the ambulatory ECG variables with clinical parameters (age, sex, LAVi, LVEF, and late gadolinium enhancement), we noted limited additional predictive value for patients with a genetic DCM (AUC of 0.772, Δ+0.004), although the clinical parameters had additional predictive value for patients with non-genetic DCM (AUC of 0.778, Δ+0.150). Notably, in genetic DCM, clinical parameters did not show predictive value for MVAE. For non-genetic DCM, only male sex and LF end-diastolic diameter indexed were significantly associated with MVAE in univariable analysis (see Supplementary material online, *Table S7*). In both groups, LVEF was not significantly associated with MVAE in univariable analysis; therefore, a sensitivity analysis was performed to contextualize the prognostic relevance of LVEF <35% in both the genetic and non-genetic population. Also within these subgroups, LVEF was not an important predictor of outcome (see Supplementary material online, *Figure S1*).

To further unravel the value of the quantification of ECG variables with ambulatory monitoring, we focused on the predictive value of the PVC burden. An increase in the burden of PVCs increases the risk of MVAE within 12 months, 36 months, and 60 months after ambulatory ECG monitoring in patients with an LP/P variant, while the risk associated with the PVC burden remains unchanged in DCM patients without an LP/P variant. Nevertheless, the presence of NSVTs has prognostic value in both groups, although the prognostic value of NSVTs in patients with a P/LP variant seems dependent on the PVC burden (*Figure 3*).

Table 2 Overview of medication, echocardiographic and cardiac magnetic resonance imaging parameters

	Genetic DCM ($n = 123$)	Non-genetic DCM ($n = 231$)	*P*-value
Age of onset, years	53 ± 13	55 ± 12	0.21
Male sex, *n* (%)	82 (67)	141 (61)	0.29
Body mass index	26.9 [23.6–30.1]	25.9 [23.7–29.9]	0.67
Medication (n = 307)			
ACEi/ARB/ARNi	75 (74.3)	174 (85.7)	0.02
Beta blockers	84 (81.6)	170 (83.3)	0.82
Mineralocorticoid receptor antagonist	39 (37.9)	84 (41.2)	0.81
Calcium channel blockers	7 (6.8)	20 (9.8)	0.55
Ivabradine	2 (1.9)	6 (2.9)	0.94
Amiodarone	7 (6.8)	6 (2.9)	0.18
Echocardiography (n = 354)			
Left ventricular ejection fraction, %	35 ± 13	38 ± 13	0.09
Indexed LF end-diastolic diameter, mm/m^2	29 ± 4	29 ± 5	0.35
Left ventricular end-systolic diameter, mm	47 ± 10	48 ± 11	0.58
Indexed left atrial volume, mL/m^2	48 ± 18	42 ± 16	**0.009**
Indexed LF mass, g/m^2	101 ± 23	107 ± 32	0.13
Cardiac magnetic resonance imaging (n = 296)			
Left ventricular ejection fraction, %	37 ± 14	39 ± 13	0.53
Indexed LF stroke volume, mL/m^2	81 ± 23	88 ± 27	0.06
Indexed LF end-diastolic volume, mL/m^2	126 ± 49	124 ± 44	0.74
Indexed LF end-systolic volume, mL/m^2	86 ± 49	80 ± 42	0.37
Indexed LF mass, g/m^2	61 ± 16	66 ± 18	0.07
Late gadolinium enhancement, *n*(%)	52 (53)	85 (43)	0.13

Values are displayed as number (percentage), mean ± standard deviation or median [interquartile range] as appropriate.

Discussion

We demonstrated a high prevalence of arrhythmias and conduction disorders on ambulatory ECG monitoring after the diagnosis of a patient with DCM, especially in the presence of a P/LP variant. Despite the significantly higher prevalence of arrhythmias, the structural and functional cardiac parameters were comparable between genetic and non-genetic DCM patients. Parameters from ambulatory ECG monitoring were important in predicting the risk of MVAE in DCM patients with a P/LP variant, whereas clinical and structural cardiac parameters were more predictive of MVAE in patients with non-genetic DCM. Our findings highlight the importance of ambulatory ECG monitoring in patients who were recently diagnosed with DCM, especially when a P/LP variant is detected.

Genetic heterogeneity of dilated cardiomyopathy

About 35% of our cohort had a P/LP variant in a gene that is robustly associated with DCM, of which 80% had at least one electrical abnormality. The high prevalence of arrhythmias and conduction disorders is not surprising, as these were previously described as predictive for the presence of a P/LP variant.[5] However, in the current study, these electrical abnormalities were detected on a single baseline ambulatory ECG analysis, showing the high yield of ECG monitoring in patients with DCM and a P/LP variant. The results show disturbances in both the atrium and the ventricle, as persistent/permanent AF, paroxysmal SVTs, PACs, NSVTs, and the number of NSVTs are all significantly more prevalent in the presence of a P/LP variant. The left atrial involvement is in line with the intrinsic atrial myopathy that can precede LF dysfunction in genetic forms of DCM.[8,9] In contrast, a high burden of atrial arrhythmias (mainly paroxysmal SVTs) on ambulatory ECG monitoring in a patient with DCM could be an indication of an underlying P/LP variant. However, information on paroxysmal SVTs is not frequently reported in studies investigating patients with genetic forms of DCM.

The genetic DCM group represents a heterogeneous group as P/LP variants in 13 different genes were detected, of which TTNtv were the most prevalent. Because there are many different affected genes, the number of patients affected by each individual gene was relatively small, which limited the possibility to analyse gene-specific data for the rarer genes. Our exploratory analysis showed a high burden of conduction disorders, atrial and ventricular arrhythmias in patients with a *LMNA* variant, while patients with a *FLNC* and TTNtv variant mainly had ventricular disturbances. The number of electrical disturbances in patients with a *MYH7* variant was less pronounced compared to the other genotypes, which is in line with a previous large *MYH7* DCM cohort study showing a low rate of electrical disturbances and MVAE.[10]

Current guidelines and recommendations

The latest guideline recommends that all patients with an established DCM undergo ambulatory ECG monitoring as part of the diagnostic process, and additional ambulatory ECG monitoring should only be considered more frequently for genotypes with a high risk of developing conduction disease and/or arrhythmias (e.g. *LMNA, PLN, FLNC*).[1] Our study showed that abnormalities are prevalent in patients with a P/LP variant and are predictive of the occurrence of

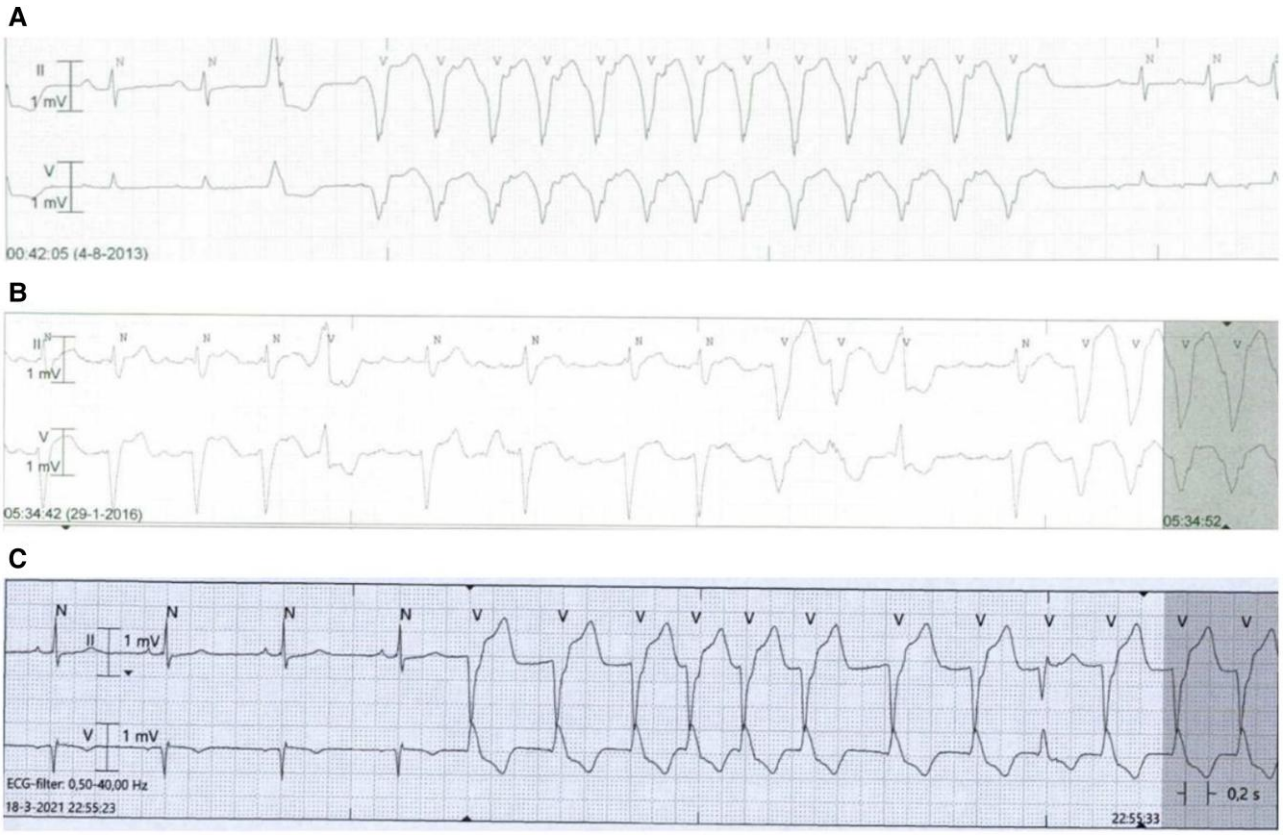
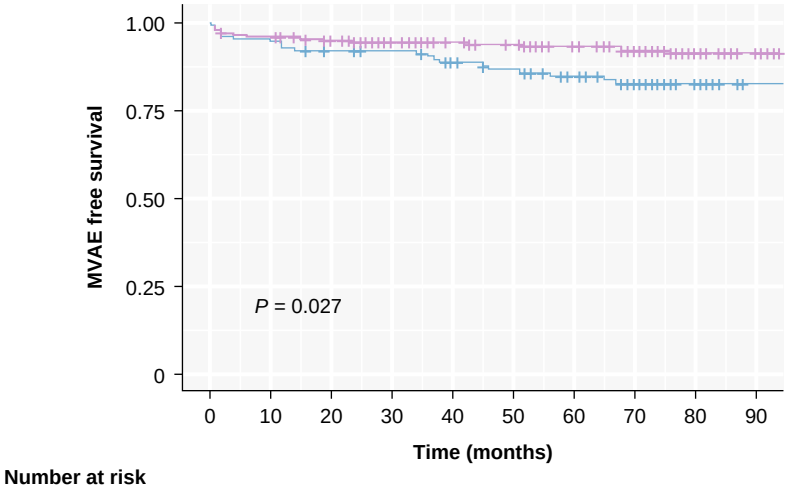


Figure 1 Example of ambulatory ECG abnormalities seen in TTN (*A*), LMNA (*B*), and FLNC (*C*). (*A*) Ambulatory ECG of a patient with a TTN mutation showing a PVC followed by a NSVT, (*B*) ambulatory ECG of a patient with a LMNA mutation showing an atrial flutter with PVC's of different morphologies and a NSVT (*C*) ambulatory ECG of a patient with a FLNC mutation showing a NSVT. NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex



Number at risk

Non-genetic DCM	231	220	211	189	179	173	163	148	127	115
Genetic DCM	123	117	110	108	101	95	84	77	66	53

Figure 2 Kaplan–Meier survival analysis of the presence of a (likely) pathogenic variant. Survival analysis based on the occurrence of MVAEs for patients with and without genetic DCM. The Kaplan–Meier curve shows that patients with genetic DCM have a significantly higher chance of developing MVAE in comparison to non-genetic DCM patients. DCM, dilated cardiomyopathy; MVAE, malignant ventricular adverse event.

Table 3 Univariable logistic regression analysis of ambulatory ECG parameters to predict malignant ventricular arrhythmic endpoints stratified on genetic aetiology

	Genetic DCM ($n = 123$)		Non-genetic DCM ($n = 231$)	
	Hazard ratio	***P*-value**	**Hazard ratio**	***P*-value**
Any abnormality	9.02 [1.22–66.7]	**0.031**	1.84 [0.69–4.93]	0.23
Heart rhythm				
Per-AF*	2.43 [1.02–5.85]	**0.047**	2.12 [0.63–7.18]	0.63
Mean heart rate	0.96 [0.92–1.01]	0.06	1.01 [0.98–1.05]	0.56
Min. heart rate	0.98 [0.93–1.02]	0.24	1.03 [0.96–1.05]	0.91
Max. heart rate	0.98 [0.96–0.99]	**0.038**	0.99 [0.98–1.01]	0.41
Conduction disorders				
Atrioventricular block*	5.18 [1.74–15.5]	**0.003**	0.05 [0–144]	0.45
Left bundle branch block	0.49 [0.07–3.59]	0.48	0.68 [0.15–3.01]	0.68
Supraventricular rhythm				
>500 PAC/24 h	1.91 [0.75–4.92]	0.18	1.05 [0.31–3.52]	0.94
Paroxysmal SVT	1.03 [0.42–2.52]	0.96	0.43 [0.06–3.21]	0.41
Number of SVT/24 h	1.02 [0.99 [1.05]	0.29	0.94 [0.66–1.35]	0.74
Longest SVT	0.98 [0.91–1.05]	0.57	1.02 [0.99–1.06]	0.23
Fastest SVT	0.98 [0.94–1.03]	0.47	1.01 [0.96–1.05]	0.93
Ventricular rhythm				
>500 PVC/24 h*	5.01 [1.72–14.6]	**0.003**	1.26 [0.58–2.75]	0.57
NSVT*	3.29 [1.47–7.41]	**0.004**	2.81 [1.23–6.43]	**0.015**
Number of NSVT/24 h	1.04 [1.01–1.06]	**0.002**	1.004 [1.001–1.007]	**0.01**
Longest NSVT	1.05 [1.01–1.09]	**0.015**	0.97 [0.84–1.12]	0.68
Fastest NSVT	1.01 [0.99–1.02]	0.38	0.99 [0.96–1.03]	0.84

bpm indicates beats per minute; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contraction; Per-AF indicates persistent/permanent atrial fibrillation; PVC, premature ventricular contraction; SVT, supraventricular tachycardia.
An asterisk (*) indicates that the variable was included in the multivariable regression model.

Table 4 Multivariable logistic regression analysis of ambulatory ECG parameters to predict malignant ventricular arrhythmic endpoints stratified on genetic aetiology

	Genetic DCM ($n = 123$)		Non-genetic DCM ($n = 231$)	
	Hazard ratio	***P*-value**	**Hazard ratio**	***P*-value**
Persistent/permanent atrial fibrillation	2.21 [0.84–5.79]	0.11	2.01 [0.59–6.84]	0.27
Atrioventricular block	4.05 [1.28–12.77]	**0.017**	0	0.98
>500 premature ventricular complexes/24 h	3.29 [1.08–10.09]	**0.038**	1.01 [0.43–2.33]	0.99
Non-sustained ventricular tachycardia	2.32 [1.09–5.41]	**0.042**	2.79 [1.16–6.77]	**0.023**
Area under the curve (AUC)	0.768 [0.668–0.868]		0.628 [0.506–0.751]	

MVAE. The exploratory analysis of different genotypes showed that non-arrhythmogenic genotypes, like TTNtv, showed a high prevalence and predictive value for the occurrence of MVAE, highlighting the need for genotype-specific studies to determine the benefit of more frequent ECG monitoring for individual genotypes.

The value of ambulatory ECG parameters to predict the risk of MVAE was prominent for DCM patients with a P/LP variant, while the additional contribution of other clinical parameters (e.g. LVEF and age) was limited in our study. The opposite was observed in patients with a non-genetic form of DCM, where the predictive value of ambulatory ECG parameters was modestly lower (AUC 0.768 vs. 0.628) and the clinical predictors carried a more important contribution in risk prediction. The limited predictive value of clinical parameters in genetic DCM might be attributed to the absence of CMR and LGE data, given that LGE is a well-established predictor of MVAE.[11] Baseline LVEF did not show predictive value, which may be explained by the dynamic nature of LVEF changes during the early phases of the disease, particularly with the up-titration of guideline-directed medical therapy. Moreover,

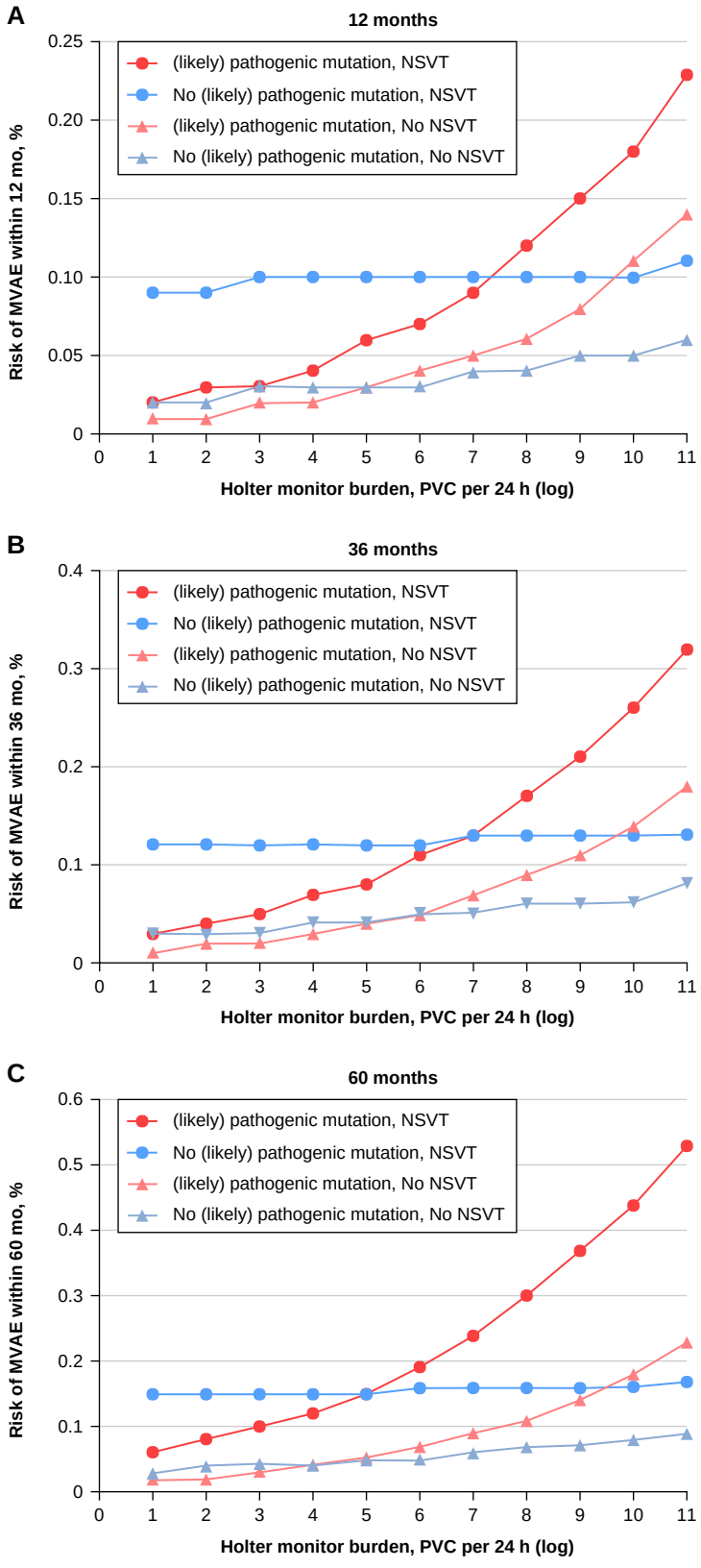


Figure 3 Association between presence of a (likely) pathogenic genetic variant and NSVT and malignant ventricular adverse events. Probability of a MVAE at 12 months (*A*), 36 months (*B*), and 60 months (*C*) from 24-h electrocardiographic ambulatory ECG monitoring during baseline diagnostic process, depending on three variables: (1) 24-h PVC burden; (2) presence or absence of NSVT; and (3) presence of a (likely) pathogenic genetic variant. MVAE, malignant ventricular adverse event; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex.

previous studies in genetic DCM have similarly reported that LVEF is not a strong predictor of MVAE.[12,13]

A genotype-based classification of patients showed higher precision in the prediction of MVAE than a phenotype-based classification.[13,14] This does not imply that clinical parameters are not relevant, but that clinical parameters predictive for MVAE differ based on genetic aetiology, which is also reflected in the composition of gene-specific risk calculators.[12,15–17] Gene-specific risk calculators are available for *LMNA*, *PLN*, *FLNC*, and *DSP*, which all include LVEF and variables derived from ECG monitoring: AV-block (*LMNA*), NSVT (*LMNA*, *FLNC*, and *DSP*), 24-h PVC burden (*PLN* and *DSP*).[12,15–17] As shown by these risk calculators, information on conduction disorders and arrhythmias derived from ECG monitoring provides important information in the risk stratification of patients with a genetic form of DCM. As we are now in the era of gene-specific risk stratification, it is important that results from routine diagnostics such as ambulatory ECG monitoring are carefully interpreted for the individual patient. A next step could be that these results will help us select the patients for novel therapies (e.g. gene therapy) that will benefit the most from treatment.[18]

Interestingly, the absolute burden of PVCs predicted the development of MVAE only in patients with a genetic variant. Previous studies have shown the prognostic value of NSVT on ambulatory ECG in DCM.[19,20] More interestingly, our study shows that in genetic forms of DCM, the prognostic value of NSVTs was influenced by the burden of PVCs, which was not observed in patients with a non-genetic form of DCM. This observation is also in line with the inclusion of PVC burden in the *PLN* and *DSP* risk calculator, showing the importance of PVC burden in genetic forms of DCM.

Future outlook

The current study focused on patients with a P/LP variant that already developed a clinical phenotype with systolic dysfunction, making it impossible to determine whether the conduction disorder or arrhythmias were present prior to the onset of systolic dysfunction. Given the high prevalence of abnormalities at baseline ECG monitoring of DCM patients, screening of asymptomatic family members with a P/LP variant will give insight into the temporal relationship between conduction disorders and/or arrhythmias and systolic dysfunction.[1] A recent study shows that patients with AF and a structurally normal heart exhibited a higher prevalence of late potentials on signal-averaged ECG, suggesting subclinical ventricular involvement and arrhythmogenic substrate in the absence of a cardiomyopathy phenotype.[21] This finding strengthens the hypothesis that electrical abnormalities could be markers for diffuse subclinical myocardial disease and electrical instability. However, a systematic analysis of ambulatory ECG monitoring in asymptomatic family members with a P/LP variant is necessary to determine the clinical value.

Previous research showed the dynamic changes detected with ECG monitoring over time in non-ischemic cardiomyopathy patients are associated with the risk of MVAE, which also highlights the importance of long-term ECG monitoring during follow-up.[22] Our current study only focused on baseline ECG monitoring data, as systematic follow-up monitoring was only performed in a minority of patients. The value of dynamic changes of ECG parameters over time could also hold predictive value for patients with (genetic) DCM, although the absolute burden of arrhythmias in patients with DCM is generally lower compared to patients with arrhythmogenic right ventricular cardiomyopathy.

Recent studies have shown the prognostic value of beat-to-beat variability of repolarization to predict NSVT and appropriate device therapy in DCM.[23] Future studies should look at the predictive value of beat-to-beat variability to predict MVAE in (genetic) DCM.

Limitations

The group of genetic DCM patients constituted a variety of genotypes combined. However, current knowledge indicates large differences between specific genotypes,[24] a finding also observed in our subgroup analysis. The number of patients per specific gene in our study is not sufficient to draw any conclusions. The data from ambulatory ECG monitoring are retrieved from the diagnostic work-up of a patient after DCM is diagnosed. Therefore, it remains unknown whether the arrhythmia and/or conduction disorder were already present before systolic dysfunction. Another limitation is that longer monitoring durations (48–72 h) were normalized to 24 h, which may influence the interpretation of infrequent events such as a single NSVT episode over for instance in 72 h. Given the limited number of events, especially within the genetic DCM group, this study should primarily be regarded as hypothesis-generating, and its results interpreted with caution. Validation of these findings in external cohorts is warranted.

Conclusion

Ambulatory ECG monitoring abnormalities are prevalent in genetic DCM patients. ECG parameters showed predictive value for MVAE risk in both genetic and non-genetic DCM, with a stronger association observed in the genetic DCM group.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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