







Arrhythmic genotypes in dilated cardiomyopathy and risk of advanced heart failure

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See the editorial comment for this article 'Arrhythmic risk and advanced heart failure in dilated cardiomyopathy: a deadly tango', by J.-B. le Polain de Waroux et al., <https://doi.org/10.1093/eurheartj/ehaf475>.

ABSTRACT

Background and aims	Certain genetic forms of dilated cardiomyopathy (DCM) entail a higher arrhythmic risk. It is unknown whether DCM patients with high-risk arrhythmic genotypes also develop more advanced heart failure (AHF) complications. AHF events were studied according to DCM genotype.
Methods	Clinical data from 1203 genotyped DCM patients were collected from 19 Spanish centres. Patients were classified into high-risk arrhythmic genotypes (LMNA, FLNC, desmosomal genes, PLN, TMEM43, RBM20), TTN, other genes, and genotype negative (Gen-). The primary endpoint was a composite of AHF events (ventricular assist device implantation, heart transplant, and AHF-related mortality). The secondary endpoint was a combination of malignant ventricular arrhythmias (MVA).
Results	A DCM-causing variant was identified in a high-risk arrhythmic gene in 185 patients (15.4%), 193 (16.0%) had variants in TTN, 134 (11.1%) in other genes, and 691 (57.4%) were Gen-. After a median follow-up of 5.7 years (interquartile range 2.9–9.1 years), AHF events occurred in 45 (24.3%) patients in the high-risk arrhythmic group, while in 25 (18.7%), 25 (13.0%), and 70 (10.1%) patients with other genotypes, TTN, and Gen-, respectively (hazard ratio 1.85, 95% confidence interval 1.31–2.61 for high-risk arrhythmic genes compared with other groups). MVA occurred in 55 patients (29.7%) (hazard ratio 2.52, 95% confidence interval 1.81–3.51 for high-risk genotypes vs other groups). High-risk arrhythmic genotype was the main independent predictor of AHF in multivariate analysis. High-risk arrhythmic genotype and late gadolinium enhancement were independent predictors of MVA.
Conclusions	Patients with high-risk arrhythmic genotypes also experience more AHF events, supporting a differential therapeutic approach in this group of patients beyond sudden death prevention.

Structured Graphical Abstract

Key Question

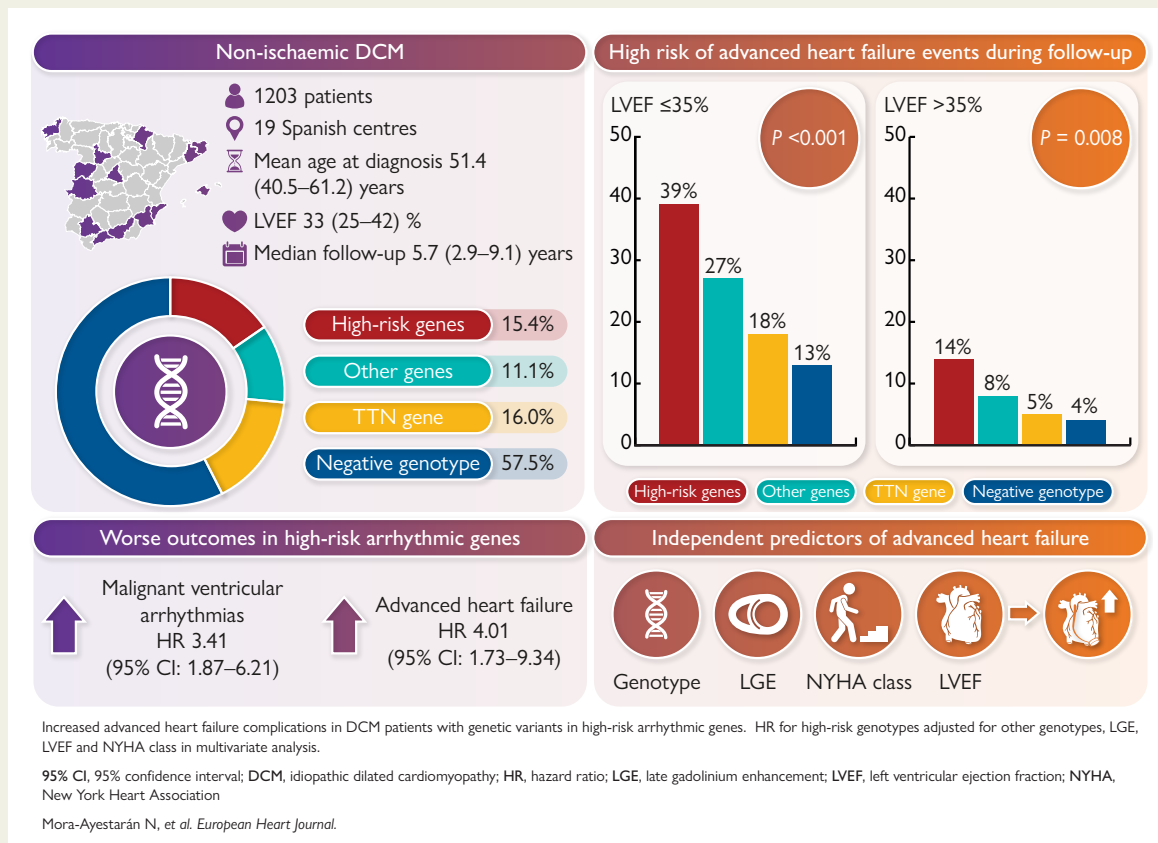
Do patients with dilated cardiomyopathy (DCM) and high-risk arrhythmic genotypes also have an increased risk of advanced heart failure events?

Key Finding

Among 1203 patients with DCM, 185 harbored high-risk arrhythmic genotypes. This patient subset not only faced a markedly elevated risk of malignant ventricular arrhythmias, but also exhibited increased burden of advanced heart failure, underscoring a particularly severe disease phenotype.

Take Home Message

DCM patients with high-risk arrhythmic genotypes require a more comprehensive therapeutic strategy addressing both arrhythmic risk and progressive heart failure.



Keywords

Dilated cardiomyopathy • Genes • Heart failure • Sudden cardiac death • Prognosis

Introduction

Non-ischemic dilated cardiomyopathy (DCM) is characterized by left ventricular dilatation and systolic dysfunction unexplained solely by abnormal loading conditions or coronary artery disease.¹ It has an estimated population prevalence of 1:250 to 1:2500 and is the most frequent cause of heart failure in the young and the leading cause of heart transplantation in the world.²

DCM constitutes a common substrate for ventricular arrhythmias and is associated with a higher risk of sudden cardiac death (SCD).^{2,3} In 30%–40% of patients, DCM is inherited as a Mendelian trait caused by genetic variants in >40 genes that encode a heterogeneous group of proteins. Such genetic heterogeneity likely contributes to the variable phenotypes and expressivity observed in patients with DCM.⁴

Advances in the genetic characterization of DCM over the last years have shown that certain DCM-associated genes (LMNA, FLNC, desmosomal, PLN, TMEM43, RBM20) exhibit a predominantly arrhythmogenic phenotype, while other genotypes (TTN, MYH7, and BAG3) have been described to exhibit a predominant heart failure phenotype in which arrhythmic events are less common.^{4–9} Based on this knowledge, the ESC guidelines and other consensus documents have promoted a more tailored approach in preventing SCD and recommend implantable cardioverter-defibrillator (ICD) implantation in patients with variants in the so-called high-risk arrhythmic genes.^{9,10}

Although there is growing evidence of differential clinical course in DCM patients according to the underlying genotype, published studies have not specifically assessed the incidence and impact of heart failure complications among patients with variants in high-risk arrhythmic

genes compared with patients with other genotypes followed in contemporary cohorts. Evaluation of advanced heart failure (AHF) events in this population constitutes a relevant gap in the field that needs to be addressed to develop personalized approaches towards heart failure management in this group of patients.

Accordingly, in the present study, we sought to study AHF events in a large multicentre cohort of genotyped patients with DCM receiving contemporary treatment with a special focus on individuals with variants in high-risk arrhythmic genes.

Methods

Study population

This was a multicentre, retrospective, observational, and longitudinal study of consecutive genetically evaluated patients with DCM recruited from inherited cardiac diseases and heart failure units at 19 Spanish hospitals between 2015 and 2022.

DCM was defined as left ventricular ejection fraction (LVEF) < 50% on echocardiogram at diagnosis in the absence of abnormal loading conditions, coronary artery disease, excessive alcohol consumption, or any other identifiable cause¹¹ (such as chemotherapy-induced cardiomyopathy or peripartum cardiomyopathy), regardless of ventricular dilation. Infiltrative cardiomyopathies were not included if the phenotype was suggestive. Patients with a family history of hypertrophic cardiomyopathy or carrying pathogenic/likely pathogenic variants in the MYBPC3 gene were also excluded as these cases might represent a late-dilated phase of hypertrophic cardiomyopathy ($n = 19$).

Only patients older than 15 years at the time of diagnosis were included. Participating individuals had been genetically tested using targeted next-generation sequencing (NGS) panels at participating institutions or at an accredited genetics laboratory with no a priori selection based on family history of DCM or clinical phenotype. Although the NGS panels could differ in the number of genes, all included >50 genes related to cardiomyopathies. Additionally, consecutive relatives with DCM ($n = 149$) who harboured a pathogenic or likely pathogenic genetic variant previously identified in a DCM proband through an NGS panel including >50 cardiomyopathy-associated disease-causing genes were included to expand individuals included in the groups with disease-causing genetic variants.

DCM was defined as familial if one or more relatives (in addition to the proband) had DCM during life or at post-mortem examination. Sporadic cases were those without a family history of DCM and where no cases of DCM were detected during familial screening in case it was performed. A relative was considered as dying of DCM if they experienced SCD or heart failure-related death with a previous diagnosis of DCM. Most of the centres had inherited cardiac disease programs and followed the recommendations of the Spanish Society of Cardiology.¹²

Demographics, symptoms, 12-lead electrocardiogram, and transthoracic echocardiography data from the first and last evaluation at participating centres were extracted from clinical records using a uniform methodology. When available, information regarding cardiac magnetic resonance (CMR) imaging was also collected. Patients underwent CMR on a 1/1.5/3.0 T magnetic resonance scanner in each centre, and subsequently, cine and late gadolinium enhancement (LGE) images from all centres were centrally evaluated in a core laboratory by two CMR experts blinded to genotype and outcomes using cvi42 CircleCVI software.

The study was approved by Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Declaration of Helsinki. The authors from each participating centre guarantee the integrity of data.

Variant classification

Variants were classified as pathogenic, likely pathogenic, unknown significance, likely benign, or benign after a systematic review by an expert

cardiologist in cardiovascular genetics using modified criteria of the American College of Medical Genetics and Genomics,¹³ as previously described.⁴ A variant was considered disease-causing if it affected a DCM-related gene and was classified as pathogenic or likely pathogenic.

The frequency of variants in the general population was extracted from the gnomAD database v2.1.1.¹⁴ We also added the information of more than 5254 index cases with no evidence of structural cardiac disease (channelopathies and aortic diseases) sequenced by NGS at Health in Code (A Coruña, Spain) with a library that included all the genes with genotype-positive variants detected in this study. This cohort was used to obtain an ancestry-specific control set, minimizing the likelihood of incorrectly categorizing variants as disease-causing if they were present in Spanish controls.

Patients were grouped into four groups based on genotype: (i) 'High-risk arrhythmic genes group' included patients harbouring pathogenic or likely pathogenic variants in LMNA, FLNC, PLN, TMEM43, RBM20, or desmosomal genes; (ii) 'TTN gene group' included patients carrying DCM-causing variants in TTN; (iii) 'Other genotypes group' included patients with pathogenic or likely pathogenic variants in other DCM-associated genes; and (iv) 'Genotype negative group' included patients without pathogenic or likely pathogenic disease-causing variants identified in the genetic testing; patients harbouring a variant of uncertain significance were also considered negative, and included in this group.

Individuals with more than one pathogenic or likely pathogenic variant in different genes ($n = 15$) were excluded from the analysis to maintain a conservative approach.

High-risk genes

The following genes were considered as high-risk arrhythmic genes: PLN, LMNA, FLNC, TMEM43, RBM20, and desmosomal genes. DCM patients with variants in PLN, DSP, LMNA, FLNC, TMEM43, and RBM20 exhibit a substantially higher rate of major arrhythmic events than other causes of DCM.^{15–25} Consequently, ESC cardiomyopathy guidelines have classified these genes as 'high-risk genotypes'.⁹ Regarding desmosomal genes, in addition to DSP, which is most frequently associated with left-sided involvement and is included in the high-risk genotype group in the ESC guidelines,⁴ DSG2, DSC2, and PKP2 have also been reported to be associated with a high rate of ventricular arrhythmias.^{26–28} Although these genes are typically associated with right ventricular involvement and the classic phenotype of arrhythmogenic right ventricular cardiomyopathy, cases with predominantly left-sided involvement have also been reported. Therefore, individuals with variants in DSG2, DSC2, and PKP2 were also included among the high-risk arrhythmic group.

Outcomes

The primary endpoint was a composite of AHF events, which included ventricular assist device implantation for refractory heart failure, heart transplant, and AHF-related deaths. The secondary endpoint was a composite of malignant ventricular arrhythmias (MVA), including SCD, aborted SCD, sustained ventricular tachycardia, and appropriate ICD interventions. Only appropriate ICD shocks to terminate ventricular tachycardia or ventricular fibrillation episodes were considered for this study (anti-tachycardia pacing therapy was not considered). All patients had planned follow-up visits every 6–12 months or more frequently if clinically indicated. Outcomes were ascertained through a systematic review of medical records, including hospitalization reports, discharge summaries, device interrogations, and, when available, death certificates. The follow-up for each patient was calculated from the date of their first evaluation at a participating centre, to the occurrence of a study endpoint, death from another cause, or the date of their most recent evaluation. Data collection was completed in December 2023.

Statistical analysis

Continuous variables are expressed as mean \pm SD or as median (interquartile range [IQR]), as appropriate. Groups were compared using Student's *t*-test or the Mann–Whitney *U* test, or analysis of variance or the

Kruskal–Wallis test when comparing more than two groups. Non-continuous categorical variables are expressed as counts (percentages) and were compared using the χ^2 or Fisher's exact test, as appropriate. The cumulative probability of an event on follow-up was estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival between groups. To assess the association of genetic status with the primary and secondary endpoints, a univariate and multivariate Cox regression model including genotype, LGE, LVEF, and New York Heart Association (NYHA) class was applied. Analyses were conducted using Stata Statistics version 15 (StataCorp). Two-tailed *P*-values $\leq .05$ defined statistical significance.

Results

A total of 1203 patients met the inclusion criteria, of whom 1054 (87.6%) were unrelated index cases and 149 (12.4%) were relatives.

A total of 512 (42.6%) patients had pathogenic or likely pathogenic variants in DCM-causing genes, 434 (36.1%) had negative genetic testing, and 257 exhibited variants of unknown significance (21.4%). By groups, 185 individuals (15.4%) exhibited variants in a high-risk arrhythmic gene, 193 (16.0%) had variants in *TTN*, and 134 (11.1%) in other DCM-associated genes.

Among those included in the high-risk arrhythmic genotype group, the most frequently involved gene was *LMNA* (51, 27.6%), followed by *DSP* (46, 24.9%), *RBM20* (40, 21.6%), *FLNC* (31, 16.8%), *TMEM43* (5, 2.7%), *DSG2* (4, 2.2%), *PKP2* (4, 2.2%), *PLN* (3, 1.6%), and *DSC2* (1, .5%). The distribution of genes in each group according to genotype is summarized in [Supplementary data online, Table S1](#).

Clinical characteristics

Demographic, clinical, and imaging baseline characteristics are presented in [Table 1](#). Male sex prevailed (67.3%), median age at diagnosis was 51.4 years (IQR: 40.5–61.2 years), and most patients were in NYHA functional class I or II (67.5%). Median baseline LVEF was 33% (IQR: 25%–42%) and 708 patients (58.9%) had an LVEF $\leq 35\%$. Atrial fibrillation was present in 182 individuals (15.1%) while 359 individuals (29.9%) had left bundle branch block.

Regarding medical treatment at last follow-up, 90.9% of the patients were treated with β -blockers; 90.2% were receiving angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or angiotensin receptor–neprilysin inhibitor (ARNI); 67.6% a mineralocorticoid receptor antagonist (MRA); and 35.6% sodium-glucose co-transporter 2 inhibitors (SGLT2i). Regarding device therapies, 544 (45.2%) patients had an ICD and 230 (19.1%) a cardiac resynchronization device at last follow-up.

Patients included in the high-risk arrhythmic genotype group were significantly younger at diagnosis than those with other genotypes (45.7 vs. 52.1 years, $P < .001$), exhibited a higher proportion of females (47.0% vs. 30.1%, $P < .001$) and a higher LVEF (40% vs 32%, $P < .001$), and lower left ventricular end-diastolic diameter (57 vs. 61 mm, $P < .001$). They were more likely to have a family history of DCM and SCD than in the other groups (74.6% vs. 47.1%, and 46.0% vs. 16.5%, respectively, both $P < .001$). Clinical characteristics of patients according to genotype groups are depicted in [Table 1](#) and [Supplementary data online, Table S2](#).

Regarding treatment, patients in the high-risk arrhythmic genotypes were treated at baseline in a lower proportion with ACEI/ARB/ARNI, beta-blockers, MRA, and SGLT2i, despite no differences were observed in the neurohormonal treatment received at last follow-up ([Table 1](#) and [S2](#)). In contrast, they received ICD more frequently during follow-up (67.6% vs. 41.2%; $P < .001$).

Outcomes

After a median follow-up of 5.7 years (IQR: 2.9–9.1 years), 165 (13.7%) patients had AHF events, and 182 (15.1%) had MVA. Clinical outcomes are summarized in [Table 2](#) and [Supplementary data online, Table S3](#).

Outcomes differed according to the underlying genotype. AHF occurred in 45 (24.3%) patients in the high-risk arrhythmic genotype group, 25 (13.0%) in *TTN* group, 25 (18.7%) in the other genotypes' group, and 70 (10.1%) in the genotype-negative group (HR: 1.85, 95% confidence interval [CI]: 1.31–2.61 for high-risk genotype patients compared with other genotypes). MVA occurred in 55 (29.7%) patients in the high-risk arrhythmic genotype group, 24 (12.4%) in the *TTN* group, 21 (15.7%) in the other genotypes group, and 82 (11.9%) in the genotype-negative group (HR: 2.52, 95% CI: 1.81–3.51 for high-risk genotype patients compared with other genotypes).

The cumulative probability of AHF and MVA during follow-up according to genotype is summarized in [Figure 1](#). Individuals with variants in high-risk arrhythmic genes showed worse prognosis, marked by both an increased number of MVA (29.7%) and also a high incidence of AHF (24.3%). However, patients with a negative genotype had better outcomes, with the lowest rate of AHF (10.1%) and MVA (11.9%). Among patients with a positive genotype, those with variants in *TTN* exhibited the best prognosis, with a rate of AHF and MVA similar to that of patients with a negative genotype. Patients with variants in other DCM-causing genes had lower rates of MVA compared with those with high-risk arrhythmic genotypes (15.7% vs. 29.7%, $P = .004$) but displayed similar rates of AHF (18.7% vs. 24.3%, $P = .227$). The distribution of MVA and AHF events by genotype, as well as the elapsed time between these events, are summarized in [Supplementary data online, Tables S4](#) and [S5](#).

Cox regression analysis

In the multivariate Cox regression analysis, the following factors were independent predictors of AHF: high-risk arrhythmic group, other genotypes group, and the presence of LGE, LVEF, and NYHA functional class \geq II ([Table 3](#)). Interestingly, carrying a variant in a high-risk arrhythmic gene was found to be the factor with the highest association with AHF (HR 4.0; 95% CI 1.73–9.34; $P = .001$).

Regarding MVA, high-risk arrhythmic genotype (HR 3.4; 95% CI 1.87–6.21; $P < .001$) and LGE (HR 3.6; 95% CI 2.15–5.91; $P < .001$) were found to be independent predictors of MVA while LVEF and NYHA functional class were not ([Table 3](#)).

Impact of genotype

In multivariate analysis, genotype was the strongest predictor of AHF and, together with LGE, the only independent predictors of MVA. When patients were stratified using LGE, NYHA functional class, and LVEF, the Harrell's C-index for MVA events was modest (.652) but substantially improved to .731 with the addition of genotype. For AHF events, the Harrell's C-index for stratification with LGE, NYHA functional class, and LVEF was already high (.760) but further increased to .786 when genotype was included.

Impact of LVEF

Classification of patients according to genotype and LVEF $\leq 35\%$ or $> 35\%$ revealed different risks of AHF and MVA among the genotype groups ([Figures 2](#) and [3](#)).

Clinical characteristics of patients included in each group can be found in [Supplementary data online, Tables S6](#) and [S7](#), and outcomes

Table 1 Baseline characteristics of the patients according to genetic subgroups

	Total n = 1203	High-risk arrhythmic genotypes n = 185	Other genotypes n = 1018	P
Demographics				
Male	810 (67.3)	98 (53.0)	712 (69.9)	<.001
Proband	1054 (87.6)	119 (64.3)	935 (91.9)	<.001
Age at diagnosis (years)	51.4 (40.5–61.2)	45.7 (35.6–55.6)	52.1 (42.0–62.3)	<.001
Age at initial evaluation (years)	53.5 (43.2–62.8)	47.2 (37.1–57.4)	54.2 (44.3–64.0)	<.001
FH of DCM	617 (51.3)	138 (74.6)	479 (47.1)	<.001
FH of SCD first-degree relative	151 (12.6)	44 (23.8)	107 (10.5)	<.001
FH of SCD non-first-degree relatives	253 (21.0)	85 (46.0)	168 (16.5)	<.001
Skeletal myopathy	42 (3.5)	9 (4.9)	33 (3.2)	.269
Previous SCD	25 (2.1)	5 (2.7)	20 (2.0)	.517
Hypertension	389 (32.3)	37 (20.0)	352 (34.6)	<.001
Dyslipidaemia	336 (27.9)	29 (15.7)	307 (30.2)	<.001
Diabetes	185 (15.4)	12 (6.5)	173 (17.0)	<.001
NYHA III-IV	389 (32.5)	40 (21.9)	349 (34.4)	.001
NYHA functional class at first evaluation				
I	417 (34.8)	88 (48.1)	329 (32.4)	
II	392 (33.7)	55 (30.1)	337 (33.2)	<.001
III	330 (27.6)	34 (18.6)	296 (29.2)	
IV	59 (4.9)	6 (3.3)	53 (5.2)	
Baseline ECG				
Atrial fibrillation	182 (15.1)	30 (16.2)	152 (14.9)	.654
AV block (third degree)	28 (2.3)	12 (6.5)	16 (1.6)	<.001
QRS duration (mm)	108 (95–140)	105 (92–120)	108 (95–140)	.022
LBBB	359 (29.9)	27 (14.8)	332 (32.7)	<.001
Abnormal T-wave inversion	253 (31.9)	37 (25.5)	216 (33.4)	.066
Low QRS voltage limb leads	171 (14.3)	55 (30.1)	116 (11.4)	<.001
Low QRS voltage precordial leads	60 (5.0)	16 (8.7)	44 (4.3)	.012
Baseline echocardiogram and CMR				
LVEF (%)	33 (25–42)	40 (29.8–46)	32 (24–40)	<.001
LVEF ≤35%	708 (58.9)	74 (40.0)	634 (62.3)	<.001
LVEDD, mm	60 (55–66)	57 (53–62.5)	61 (55–66)	<.001
MR moderate/severe	378 (32.5)	50 (27.9)	328 (33.3)	.158
RVSD (any degree)	237 (21.6)	28 (16.6)	209 (22.6)	.083
LGE	145 (24.8)	26 (34.7)	119 (23.3)	.034
Drug treatment at initial evaluation				
B-blockers	971 (81.5)	138 (75.4)	833 (82.6)	.020
ACEI/ARB/ARNI	1067 (88.7)	155 (83.8)	912 (89.6)	.022
MRA	484 (40.9)	59 (32.2)	425 (42.2)	.012
SGLT2i	79 (7.0)	5 (2.8)	74 (7.7)	.019

Continued

Table 1 Continued

	Total n = 1203	High-risk arrhythmic genotypes n = 185	Other genotypes n = 1018	P
Treatment at last evaluation				
B-blockers	1073 (90.9)	165 (91.7)	908 (90.8)	.709
ACEI/ARB/ARNI	1084 (90.2)	168 (91.3)	916 (90.0)	.579
MRA	796 (67.6)	116 (64.4)	680 (68.1)	.330
SGLT2i	355 (35.6)	52 (33.1)	303 (36.1)	.479
ICD	544 (45.2)	125 (67.6)	419 (41.2)	<.001
CRT	230 (19.1)	31 (16.8)	199 (19.6)	.374

Values are n (%). Continuous variables are expressed as mean \pm standard deviation (SD) or as median (IQR), as appropriate. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; FH, family history; HF, heart failure; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MR, mitral regurgitation; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; PASP, pulmonary artery systolic pressure; RVSD, right ventricular systolic dysfunction; SCD, sudden cardiac death; SGLT2i, sodium-glucose co-transporter type 2 inhibitors.

Table 2 Outcomes and Events during follow-up according to underlying genetic

	Total n = 1203	High-risk arrhythmic genotype n = 185	Other genotypes n = 1018	P
Composite MVA	182 (15.1)	55 (29.7)	127 (12.5)	<.001
Sustained VA	113 (9.4)	37 (20.0)	76 (7.5)	<.001
Appropriate ICD therapy	113 (20.8)	33 (26.4)	80 (19.1)	.077
SCD	38 (3.2)	14 (7.6)	24 (2.4)	<.001
MVA-related mortality	24 (2.0)	10 (5.4)	14 (1.4)	<.001
Composite AHF	165 (13.7)	45 (24.3)	120 (11.8)	<.001
Heart transplant	114 (9.5)	34 (18.4)	80 (7.9)	<.001
LVAD implantation	31 (2.6)	14 (7.6)	17 (1.7)	<.001
HF-related mortality	53 (4.4)	10 (5.4)	43 (4.2)	.471
All-cause mortality	152 (12.7)	30 (16.3)	122 (12.0)	.107
HF hospitalization	253 (21.0)	51 (27.6)	202 (19.8)	.018
LVRR	537 (45.0)	51 (27.7)	486 (48.1)	<.001

Values are n (%). Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. AHF, advanced heart failure; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVRR, left ventricular reverse remodelling; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death including aborted SCD; VA, ventricular arrhythmia.

are summarized in [Supplementary data online, Tables S8 and S9](#). Cox regression analyses to predict the risk of AHF and MVA according to genotype and LVEF subgroups (LVEF \leq 35% vs. >35%) are presented in [Table 4](#).

Patients with LVEF \leq 35% had a higher risk of AHF than those with LVEF >35% in all the genotype groups. However, this risk was different depending on the genotype: high-risk arrhythmic genotypes (HR 9.6, 95% CI 4.81–19.29, $P < .001$) had the higher risk, followed by other positive genotypes (HR 7.0, 95% CI 3.35–14.60, $P < .001$), *TTN* (HR 4.5, 95% CI 2.18–9.42, $P < .001$), and genotype negative (HR 3.4, 95% CI 1.78–6.43, $P < .001$). In patients with LVEF >35%, compared with those with a negative genotype, only high-risk genotypes were

associated with an increased risk of AHF events (HR 2.8, 95% CI 1.30–6.06, $P = .009$).

Regarding MVA, patients with LVEF \leq 35% and a positive genotype had a higher risk of events, except for the *TTN* group. Nevertheless, this risk was different depending on the genotype: high-risk arrhythmic genotypes exhibited the higher risk (HR 4.9, 95% CI 2.87–8.37, $P < .01$), followed by carriers of DCM causal variants in other genes (HR 2.1, 95% CI 1.10–4.00, $P = .024$). In patients with LVEF >35%, compared with those with a negative genotype, only carriers of high-risk arrhythmic genotypes had an increased risk of developing arrhythmic events (HR 1.9, 95% CI 1.11–3.40, $P = .020$).

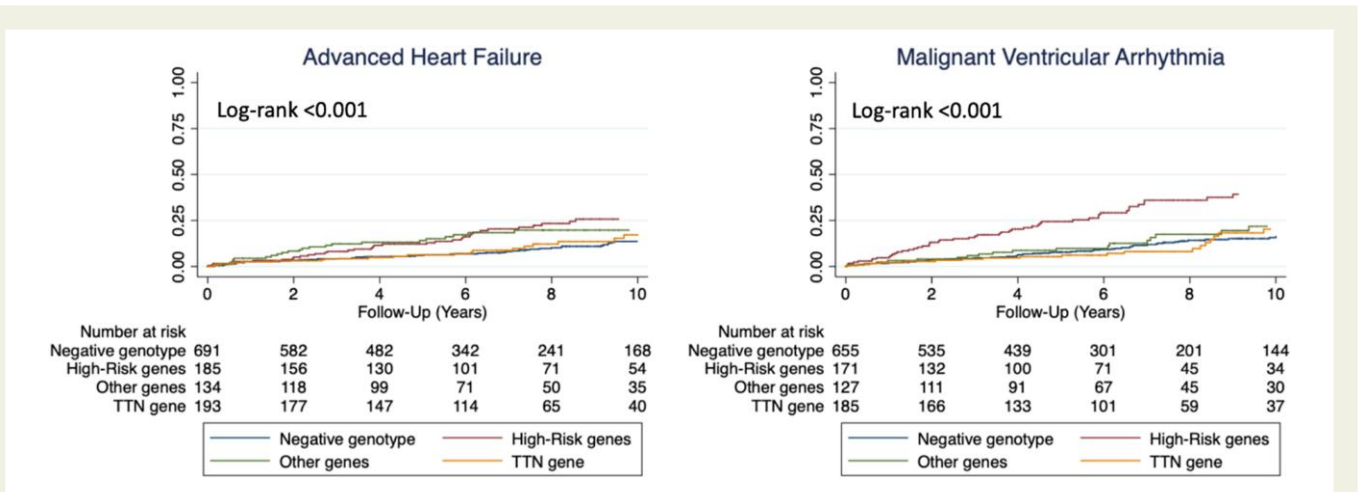


Figure 1 Advanced heart failure and malignant ventricular arrhythmia according to genetic subgroup

Table 3 Cox analysis of LVEF, functional class, genotype and LGE to predict outcomes

	Hazard ratio	95% CI	P
Advanced Heart Failure			
Genotype			
Negative genotype	Ref.		
High-risk genotypes	4.01	1.73–9.34	.001
Other genotypes	3.20	1.29–7.90	.012
TTN gene	1.51	.58–3.92	.395
LGE			
Negative	Ref.		
Positive	3.29	1.70–6.38	<.001
LVEF	.96	.93–.996	.028
NYHA class			
NYHA I	Ref.		
NYHA \geq II	2.40	1.01–5.70	.046
Malignant ventricular arrhythmia			
Genotype			
Negative genotype	Ref.		
High-risk genotypes	3.41	1.87–6.21	<.001
Other genotypes	.95	.37–2.45	.912
TTN gene	1.00	.47–2.11	.997
LGE			
Negative	Ref.		
Positive	3.57	2.15–5.91	<.001
LVEF	.98	.96–1.01	.183
NYHA class			
NYHA I	Ref.		
NYHA \geq II	1.29	.73–2.29	.378

Values are n (%). LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

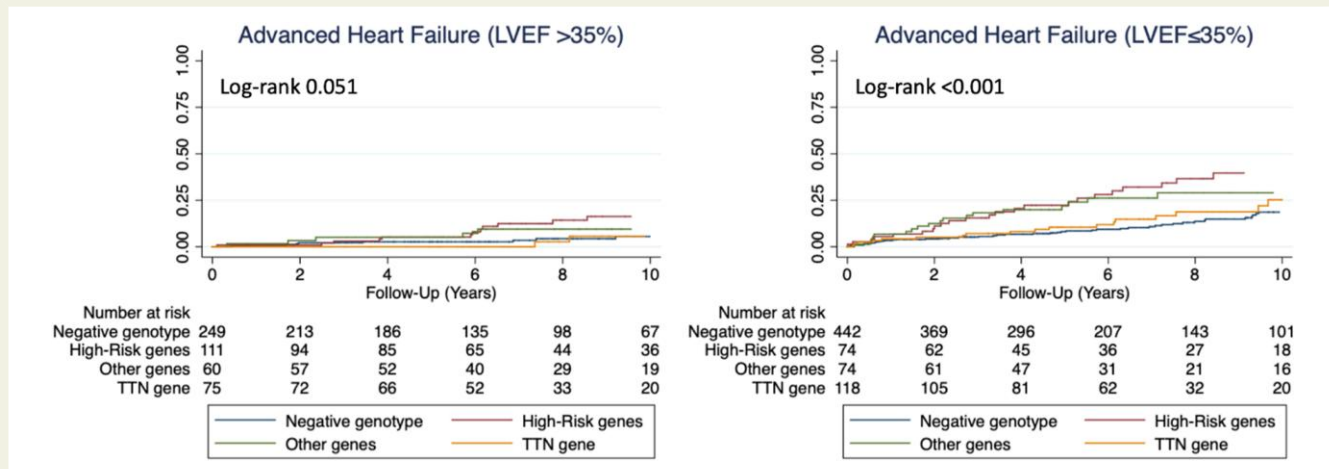


Figure 2 Advanced heart failure according to genotype and LVEF ≤35% or >35

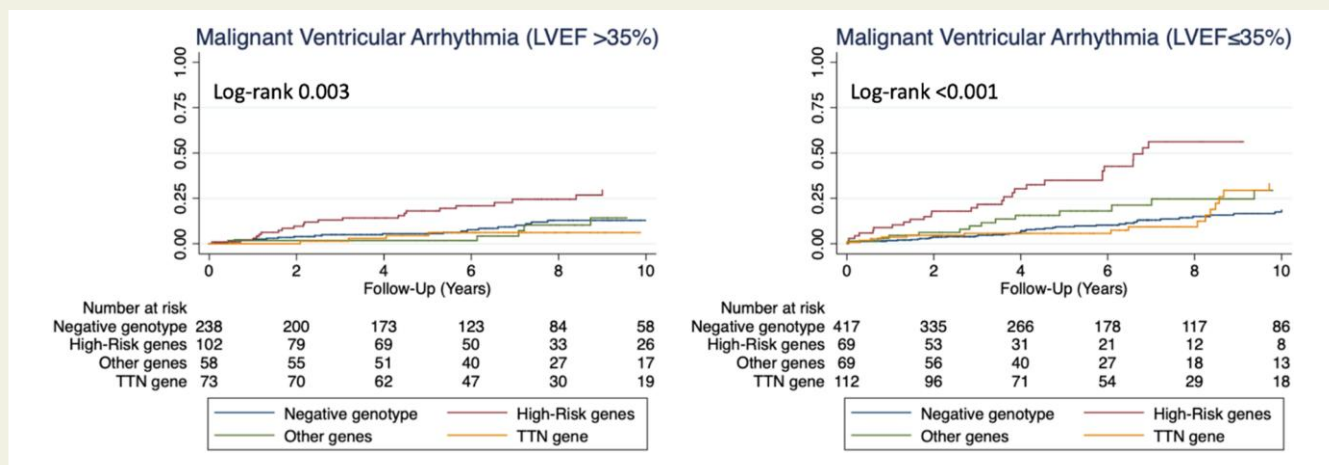


Figure 3 Malignant ventricular arrhythmia according to genotype and LVEF ≤35% or >35%

When analysing MVA according to genotype and LVEF, considering an LVEF threshold of 45% (as this is the LVEF threshold that has been proposed to consider an ICD in individuals with variants in high-risk arrhythmic genes¹⁰), patients with variants in high-risk arrhythmic genes and an LVEF >45% maintained a significantly increased risk of arrhythmic events compared with those with a negative genotype (HR 2.6, 95% CI 1.16–6.00, $P = .02$). Cox regression analyses to predict the risk of AHF and MVA according to genotype and LVEF subgroups (LVEF <45% vs. ≥45%) are presented in [Supplementary data online, Table S10](#).

Discussion

In this large multicentre study of genotyped DCM patients, we found that subjects with pathogenic or likely pathogenic variants in high-risk arrhythmic genes exhibit a high rate of AHF complications, including heart failure hospitalizations, left ventricular assist device (LVAD) implantation, or heart transplant ([Structured Graphical Abstract](#)). Although the association of genetic variants in these genes with MVA has been largely described, the impact of these genotypes on

AHF events has not been previously investigated. The importance of the association found between variants in high-risk arrhythmic genes and AHF was further supported by the fact that high-risk arrhythmic genotypes was the main factor associated with AHF in multivariate analysis. Interestingly, patients with high-risk arrhythmic variants exhibited more AHF events despite higher LVEF and less dilated left ventricles at baseline than DCM patients with other genotypes. Moreover, when analysing AHF events taking into consideration LVEF, carrying a genetic variant in a high-risk arrhythmic gene remained associated with developing heart failure complications even in patients with mild systolic dysfunction at baseline. Overall, these findings have important implications regarding the treatment and follow-up of DCM patients with high-risk arrhythmic gene variants beyond earlier ICD implantation.

Genotype as a predictor of AHF outcomes

Traditionally, arrhythmic complications have been the focus of therapeutic management of patients with genetic variants in a group of specific genes that include LMNA, DSP, RBM20, or PLN among others.

Table 4 Cox regression to predict Advanced Heart Failure and Malignant Ventricular Arrhythmia according to genotype and LVEF (LVEF ≤35% vs. >35%)

	Hazard ratio	95% CI	P
Advanced heart failure			
Negative genotype and LVEF > 35%	Ref.		
High-risk genotypes and LVEF > 35%	2.81	1.30–6.06	.009
Other genotypes and LVEF > 35%	1.57	.55–4.53	.400
TTN gene and LVEF > 35%	1.12	.36–3.53	.843
Negative genotype and LVEF ≤ 35%	3.37	1.78–6.43	<.001
High-risk genotypes and LVEF ≤ 35%	9.63	4.81–19.29	<.001
Other genotypes and LVEF ≤ 35%	6.99	3.35–14.60	<.001
TTN gene and LVEF ≤ 35%	4.54	2.18–9.42	<.001
Malignant ventricular arrhythmia			
Negative genotype and LVEF > 35%	Ref.		
High-risk genotypes and LVEF > 35%	1.94	1.11–3.40	.020
Other genotypes and LVEF > 35%	.62	.24–1.61	.327
TTN gene and LVEF > 35%	.43	.15–1.23	.116
Negative genotype and LVEF ≤ 35%	1.21	.76–1.93	.430
High-risk genotypes and LVEF ≤ 35%	4.90	2.87–8.37	<.001
Other genotypes and LVEF ≤ 35%	2.10	1.10–4.00	.024
TTN gene and LVEF ≤ 35%	1.69	.94–3.05	.079

Reference group: DCM patients with LVEF >35% and negative genotype.

Although heart failure events have not been traditionally under the scope in patients with these genotypes, a closer look into the studies reporting natural history of cohorts of patients with variants in these genes reveals that AHF also contribute to the disease burden in these patients. Studies with LMNA-related DCM patients showed a high risk of AHF, as 19% of the patients required a heart transplant during a mean follow-up of 7.8 years²⁹ and 22% presented AHF at 7 years.³⁰ Moreover, RBM20-related DCM has been recently described to have a non-negligible rate of AHF events particularly among males, with 14% of patients requiring LVAD, heart transplantation, or died due to heart failure after a median follow-up of 7.2 years.²⁴

Additionally, in a recent multicentre study of patients with DSP variants, 4.8% of the patients underwent a heart transplant over a median follow-up of 3.7 years.¹⁷

Our data are consistent with previous findings and bring AHF complications in these genotypes to the front line by analysing these events in a wide multicentre cohort of patients receiving modern heart failure therapies. In fact, our data suggest that the higher rate of AHF complications observed among patients with high-risk arrhythmic genes might be in relation to a lower response to neurohormonal treatment because only 27.7% of patients with variants in high-risk arrhythmic genes exhibited left ventricular reverse remodelling compared with a remodelling rate of around 50% observed in genotype-negative patients and in patients with variants in TTN.

These findings are consistent with previous studies that have shown a different rate of left ventricular reverse remodelling according to the

underlying genotype,^{4,31} with the highest rate of reverse remodelling in TTN-truncating variants^{5,6} and genotype-negative groups, and the lower rates in other positive genotypes, particularly in desmosomal and nuclear envelope groups.⁴

The grim prognosis observed in DCM patients with high-risk arrhythmic genotype is particularly relevant if we take into consideration that in our cohort, DCM patients with these genotypes were younger at diagnosis, had a better functional class (most of them asymptomatic or mildly symptomatic), and exhibited higher LVEF and lower end-diastolic diameters at baseline than DCM patients with other genotypes.

Our study also confirms previous reports that suggested a more benign clinical course of DCM caused by TTN-truncating variants, with lower number of AHF events compared with other positive genotypes.^{5,6} Nevertheless, after 10 years of follow-up, we observed an increase in AHF events among these patients. This long-term rebound might be in relation to the recent description of LVEF deterioration in up to 39% of patients with TTN-truncating variants who exhibited an initial favourable LVEF recovery.⁶

Regarding other genotypes, patients with variants in other genes like BAG3⁸ and MYH7⁷ have been traditionally considered at high risk of AHF events. Our study confirms the high rate of AHF events in these subjects with a high number of patients requiring LVAD implantation or heart transplant, despite the AHF complications rate being lower than in the high-risk arrhythmic genes group.

Genotype as a predictor of arrhythmic outcomes

Unsurprisingly, our study confirms that patients with high-risk arrhythmic genotypes show higher risk of MVA in consonance with previous studies where high-risk arrhythmic genes (LMNA, FLNC, PLN, TMEM43, RBM20, desmosomal genes) were analysed independently.^{15–25}

Classically, LVEF <35% has been used as the threshold to indicate ICD implantation in DCM.^{32,33} However, in our study, LVEF <35% threshold failed as a predictor of MVA in DCM patients with high-risk arrhythmic genetic variants. In fact, patients with LVEF >35% and high-risk arrhythmic genotypes showed a significantly increased risk of developing arrhythmic events (HR 1.9, 95% CI 1.11–3.40, $P = .020$). These findings support recent guideline recommendations for ICD implantation in patients with high-risk arrhythmic genotypes and a mildly reduced LVEF.^{9,10}

Of note, although an LVEF <45% has been proposed as an appropriate cut-off value to select patients with high-risk genotypes who should undergo ICD implantation,¹⁰ in our cohort, patients with LVEF \geq 45% exhibited almost three times higher rate of MVA than genotype-negative individuals. Our findings highlight the importance of genotype for arrhythmic risk stratification in DCM and support an even higher LVEF threshold for ICD implantation in these patients.

Added value of genotype as a risk factor

In our study genotype emerged as the strongest predictor of AHF events and, along with LGE, an independent determinant of arrhythmic risk. Furthermore, our findings suggest that genetic information enhances risk stratification for both arrhythmic and AHF events. When genotype was added to the risk factors used in daily clinical practice (LVEF, NYHA functional class, LGE), risk stratification improved.

Clinical implications

Our study adds to the body of evidence showing that genetic testing is essential to adequately stratify DCM patients and define their follow-up. Patients with high-risk arrhythmic genotypes have high risk of suffering AHF complications as well as ventricular arrhythmias. Based on our findings, patients and relatives with variants in these genes should be followed closer with early referral to AHF units. Moreover, given the poor outcomes observed, neurohormonal treatment should be early initiated and aggressively titrated in these patients even in individuals with mild left ventricular dysfunction. A sizeable proportion of patients with a high-risk arrhythmic genotype are young people who are asymptomatic or have mild symptoms at diagnosis and show mild left ventricular dysfunction. Efforts should be put into define the most appropriate approach to early diagnose and treat these subjects. Given the improvement in survival derived from early ICD implantation in these patients, heart failure is expected to become their leading cause of death. Therefore, our findings highlight an important unmet need: the need of developing specific therapies to tackle and prevent heart failure complications in patients affected by these DCM subtypes.³⁴ Initial gene therapy trials being developed for DCM caused by variants in high-risk arrhythmic genes might be tempted of focusing on arrhythmic events but, based in our findings, a more traditional outcomes' approach considering hospitalizations and heart failure mortality might be equally or more powerful to show positive results and allow drug development.

Limitations

The study's limitations stem from its observational nature and retrospective design. A potential influence of baseline treatment differences

cannot be excluded. This design carries an inherent risk of misclassification in outcome adjudication. Serial LVEF data were not available to assess temporal changes. While the main DCM genes were assessed in all cases, the genes incorporated in NGS target panels differed among centres and over time, reflecting the evolving understanding of DCM genetics over the past decade.

Furthermore, participating centres are specialized in inherited cardiac diseases and heart failure units, which may result in a higher proportion of patients with advanced phenotypes. Therefore, the findings may not be generalizable to other healthcare settings.

Conclusions

Patients with DCM and pathogenic or likely pathogenic variants in high-risk arrhythmic genes exhibit a poor prognosis with a high rate of AHF events. Specific treatment for this group of patients should go beyond MVA prevention and incorporate early and tailored therapeutic approaches to prevent heart failure complications.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Data Availability

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

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Ethical Approval

The study was approved by the Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Declaration of Helsinki. The authors from each participating centre guarantee the integrity of data.

Pre-registered Clinical Trial Number

Not applicable.

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