Mora-Ayestarán N, Ochoa JP, Espinosa-Castro MÁ, Navarro-Peñalver M, Villacorta E, Crespo-Leiro MG, Climent-Payá V, Lacuey-Lecumberri G, Peña-Peña ML, Bermúdez-Jiménez FJ, García-Pinilla JM, Mogollón-Jiménez MV, Limeres-Freire J, García-Álvarez A, Bayés-Genís A, Palomino-Doza J, Tirón C, Ripoll-Vera T, López J, Brion M, Vilches-Soria S, Sabater-Molina M, García-Berrocal B, Larrañaga-Moreira JM, García-Álvarez MI, Basurte-Elorz MT, Llamas-Gómez H, Méndez-Fernández I, Garrido-Bravo IP, González-López E, Gallego-Delgado M, Barriales-Villa R, Lara-Pezzi E, García-Pavía P, Domínguez F. Association of genotype with treatment response and prognosis in dilated cardiomyopathy. ***Rev Esp Cardiol (Engl Ed)***. 2025 Oct 9:S1885-5857(25)00273-7. English, Spanish. doi: 10.1016/j.rec.2025.10.002. Epub ahead of print. PMID: 41067410.

which has been published in final form at

https://doi.org/10.1016/j.rec.2025.10.002

Rev Esp Cardiol. 2025;xx(x):xxx–xxx

Original article

Association of genotype with treatment response and prognosis in dilated cardiomyopathy

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https://doi.org/10.1016/j.rec.2025.10.002

Please cite this article in press as: Mora-Ayestarán N, et al. Association of genotype with treatment response and prognosis in dilated cardiomyopathy. *Rev Esp Cardiol.* 2025. https://doi.org/10.1016/j.rec.2025.10.002

Article history:
Received 5 June 2025
Accepted 24 September 2025

Keywords:
Dilated cardiomyopathy
Genetics
Remodeling
Left ventricular ejection fraction
Prognosis

ABSTRACT

Introduction and objectives: Left ventricular reverse remodeling (LVRR) is a key therapeutic goal in dilated cardiomyopathy (DCM). However, its genetic predictors and prognostic impact remain uncertain.
Methods: We analyzed genotyped DCM patients with serial echocardiograms from the Spanish DCM study. The main objective was to assess the influence of genotype on LVRR, defined by improvement in ejection fraction within 12 ± 6 months. Secondary endpoints included major adverse cardiovascular events, end-stage heart failure (HF), and major ventricular arrhythmias.
Results: A total of 711 patients were included (67% male, mean age 50.8 years, baseline ejection fraction 31%, 44% genotype positive). LVRR occurred in 39% of genotype-positive vs 47% of genotype-negative patients ($P = .036$). Independent predictors of LVRR were TTN variants, lower baseline ejection fraction, and HF admission at diagnosis. In contrast, desmosomal, nuclear envelope and motor sarcomeric gene variants were associated with a lower likelihood of LVRR. During a median follow-up of 4.5 years, 26% of patients with initial LVRR showed subsequent deterioration, which was more frequent among genotype-positive individuals (32% vs 22%, $P = .054$). Compared with patients with sustained LVRR, those with deterioration had worse outcomes, including higher rates of major cardiovascular events (25% vs 7%), end-stage HF (18% vs 1%), and ventricular arrhythmia (12% vs 4%) (all $P < .05$).
Conclusions: Genotype is a major determinant of both initial and long-term LVRR. Loss of ejection fraction improvement is common and strongly associated with adverse outcomes.

Asociación del genotipo con la respuesta al tratamiento y pronóstico de la miocardiopatía dilatada

Palabras clave:
Miocardiopatía dilatada
Genética
Remodelado
Fracción de eyección del ventrículo izquierdo
Pronóstico

RESUMEN

Introducción y objetivos: El remodelado inverso del ventrículo izquierdo (RIVI) es un objetivo terapéutico en la miocardiopatía dilatada (MCD). Se desconocen sus predictores genéticos y su impacto pronóstico a largo plazo.
Métodos: Se analizó a pacientes con MCD genotipada del estudio español con ecocardiogramas seriados. El objetivo principal fue evaluar la influencia del genotipo en el RIVI, definido como mejoría de la fracción de eyección en 12 ± 6 meses. Los objetivos secundarios incluyeron eventos cardiovasculares mayores, insuficiencia cardiaca (IC) avanzada y arritmias ventriculares mayores.
Resultados: Se incluyó a 711 pacientes (el 67% varones, edad media de 50,8 años, fracción de eyección inicial del 31%, y el 44% de genotipo positivo). El RIVI se observó en el 39% de los portadores y el 47% de los no portadores (p = 0,036). En el análisis multivariado, variantes en TTN, menor fracción de eyección basal y hospitalización por IC al diagnóstico se asociaron con mayor probabilidad de RIVI, mientras que mutaciones desmosómicas, de membrana nuclear y sarcoméricas, con menor RIVI. Tras un seguimiento de 4,5 años, el 26% de los pacientes con RIVI inicial presentaron deterioro posterior de la fracción de eyección, más frecuente en portadores (el 32 frente al 22%; p = 0,054). Estos pacientes tuvieron peor pronóstico que aquellos con RIVI mantenido: más eventos cardiovasculares mayores (el 25 frente al 7%), IC avanzada (el 18 frente al 1%) y arritmias ventriculares (el 12 frente al 4%) (todos, p < 0,05).
Conclusiones: El genotipo es determinante del RIVI inicial y sostenido. La pérdida de mejoría funcional es frecuente y se asocia con un peor pronóstico.

Abbreviations

DCM: dilated cardiomyopathy
ESHF: end-stage heart failure
LVEF: left ventricular ejection fraction
LVRR: left ventricular reverse remodeling
MACE: major adverse cardiovascular events
MVA: major ventricular arrhythmias

INTRODUCTION

Nonischemic dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and systolic dysfunction that cannot be attributed to abnormal loading conditions or coronary artery disease.[1] It has an estimated prevalence of 1:250 to 1:2500 in the general population and is the most frequent cause of heart failure in the young, the leading cause of heart transplantation worldwide, and a common substrate for ventricular arrhythmias and sudden cardiac death (SCD).[1–3]

Recovery of left ventricular function is a primary objective of pharmacological therapies in heart failure with reduced ejection fraction, as the absence of left ventricular reverse remodeling (LVRR) is an early predictor of mortality.[4] However, not all patients respond to medical treatment, and even among those who initially achieve LVRR, some experience LVEF worsening in the long-term.[5]

Assessing treatment response is therefore essential, as clinical decisions regarding treatment strategies, such as eligibility for implantable cardioverter-defibrillator (ICD) therapy, are still largely based on the presence of significant LV dysfunction.

A genetic substrate can be identified in 25% to 40% of cases of nonischemic DCM,[6] and growing evidence suggests that the

Please cite this article in press as: Mora-Ayestarán N, et al. Association of genotype with treatment response and prognosis in dilated cardiomyopathy. *Rev Esp Cardiol.* 2025. https://doi.org/10.1016/j.rec.2025.10.002

underlying genotype has a substantial impact on treatment response and clinical course.[7–11] However, the long-term impact of genotype at long-term after initial recovery remains unclear, and little is known about the clinical course and prognosis in patients who experience early recovery of left ventricular function.

Accordingly, we sought to evaluate the influence of genotype during early follow-up, identify factors associated with LVRR, and assess long-term systolic function after initial recovery in a large cohort of genotyped DCM patients.

METHODS

Study population

This was a multicenter, retrospective, observational, and longitudinal study of consecutive genetically evaluated patients with DCM recruited from inherited cardiac disease and heart failure units at 19 Spanish hospitals between 2015 and 2022. Patients underwent serial echocardiography at baseline and at 12 ± 6 months (intermediate echocardiogram). An additional echocardiogram at the last follow-up visit was collected if available.

DCM was defined as left ventricular ejection fraction (LVEF) < 50% on echocardiography in the absence of abnormal loading conditions, coronary artery disease, excessive alcohol intake, or other identifiable causes.[1] Patients diagnosed in infancy (< 1 year of age) were excluded, given that the etiology, natural history, and outcomes of infant-onset cardiomyopathies can differ substantially from those in older children, adolescents, and adults.[12]

Participating individuals had been genetically tested using targeted next-generation sequencing (NGS) panels at participating institutions or at an accredited genetics laboratory. Although the NGS panels could differ in the number of genes, all included > 50 genes related to cardiomyopathies. Additionally, consecutive relatives with DCM (n = 93) who harbored a pathogenic or likely pathogenic variant previously identified in a DCM proband through an NGS panel including > 50 cardiomyopathy-associated disease-causing genes were included to enrich the number of DCM patients with a positive genotype. Demographics, symptoms, 12-lead electrocardiogram, and transthoracic echocardiogram data were collected from clinical records at each participating center using standardized methodology.

The study was approved by the *Hospital Universitario Puerta de Hierro* ethics committee, which waived the requirement for informed consent. The study conformed to the principles of the Declaration of Helsinki. Data integrity was ensured by the investigators at each participating center.

Genotype-based classification and gene clusters

Genetic variants were centrally classified as pathogenic (P), likely pathogenic (LP) or variant of unknown significance after a systematic review by a cardiologist expert in cardiovascular genetics using modified criteria of the American College of Medical Genetics and Genomics.[13] A variant was considered disease-causing if it affected a DCM-related gene and was classified as P/LP. Patients harboring P/LP variants were considered"'genotype-positive" (G +), and those harboring variant of unknown significance variants or with a negative NGS panel were considered "genotype-negative" (G-).

Genes were clustered into functional gene groups based on similar common functions, involvement in biological processes, localization to subcellular compartments, and other shared properties based on consolidated scientific evidence from the literature and available biological databases as previously described.[14] Because of its specific characteristics of frequency in DCM, *TTN* was considered as a separate group. Functional gene groups included the following: *a)* structural cytoskeleton/Z-disk; *b)* desmosomal; *c)* nuclear envelope; *d)* motor sarcomeric; *e) TTN*; and *f)* other genes. Individuals with > 1 pathogenic or likely pathogenic variant (n = 8) were excluded from the functional gene group analysis to maintain a conservative approach.

LVRR definition

LVRR was defined as either left ventricular normalization (LVEF improvement to ≥ 50% with an absolute increase of ≥ 5% LVEF from baseline evaluation on echocardiogram) or an absolute increase in LVEF of ≥ 10%, as previously described.[8,15–17] Persistent LVRR at long-term among those patients who had a favorable initial response was defined as improvement or stability (± 5%) in LVEF in the last follow-up echocardiogram compared with the mid-term evaluation.

Outcomes

Our primary objective was to analyze the impact of genotype on LVRR and evaluate the factors associated with LVRR.

Additionally, we evaluated the clinical impact of persistency of LVRR at long-term. Clinical outcomes were evaluated according to the presence or absence of LVRR at 12 ± 6 months. Among patients with a positive LVRR at 12 ± 6 months, outcomes were further assessed according to the persistence or loss of LVRR at the last follow-up. The clinical objectives considered were a composite of major adverse cardiovascular events (MACE), a composite of major ventricular arrhythmias (MVA), and a composite of end-stage heart failure (ESHF). The MACE composite objective included cardiovascular death, ESHF, and MVA. ESHF included ventricular assist device implantation for refractory heart failure, heart transplant, and ESHF-related mortality. MVA included SCD or aborted SCD, sustained ventricular tachycardia, and appropriate ICD interventions. Only appropriate ICD shocks to terminate ventricular tachycardia or ventricular fibrillation episodes were considered for the purpose of this study (anti-tachycardia pacing therapy was not considered).

All patients had planned reviews at participating centers every 6 to 12 months or more frequently if clinically indicated. A detailed flow chart of the study is presented in figure 1.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD) or as median [interquartile range (IQR)], as appropriate. Groups were compared using the Student *t* test, the Mann-Whitney U test, the ANOVA test, or the Kruskal-Wallis test when comparing more than 2 groups. Non-continuous categorical variables were expressed as counts (percentages) and compared using the chi-square test or Fisher's exact test, as appropriate.

Logistic regression analysis was applied to determine the association of genotype and clinical variables with LVRR. The multivariate analysis was performed using the forward stepwise logistic regression method and a significance level of 0.05. Only patients with complete data for all covariates included in the final model were analyzed (complete-case analysis; n = 636). Clinical, echocardiographic, and genetic parameters that were statistically significant in the univariate analysis were included ($P < .05$). The presence of negative T waves was not included due to collinearity. Treatment with SGLT2 inhibitors was not included since quadruple

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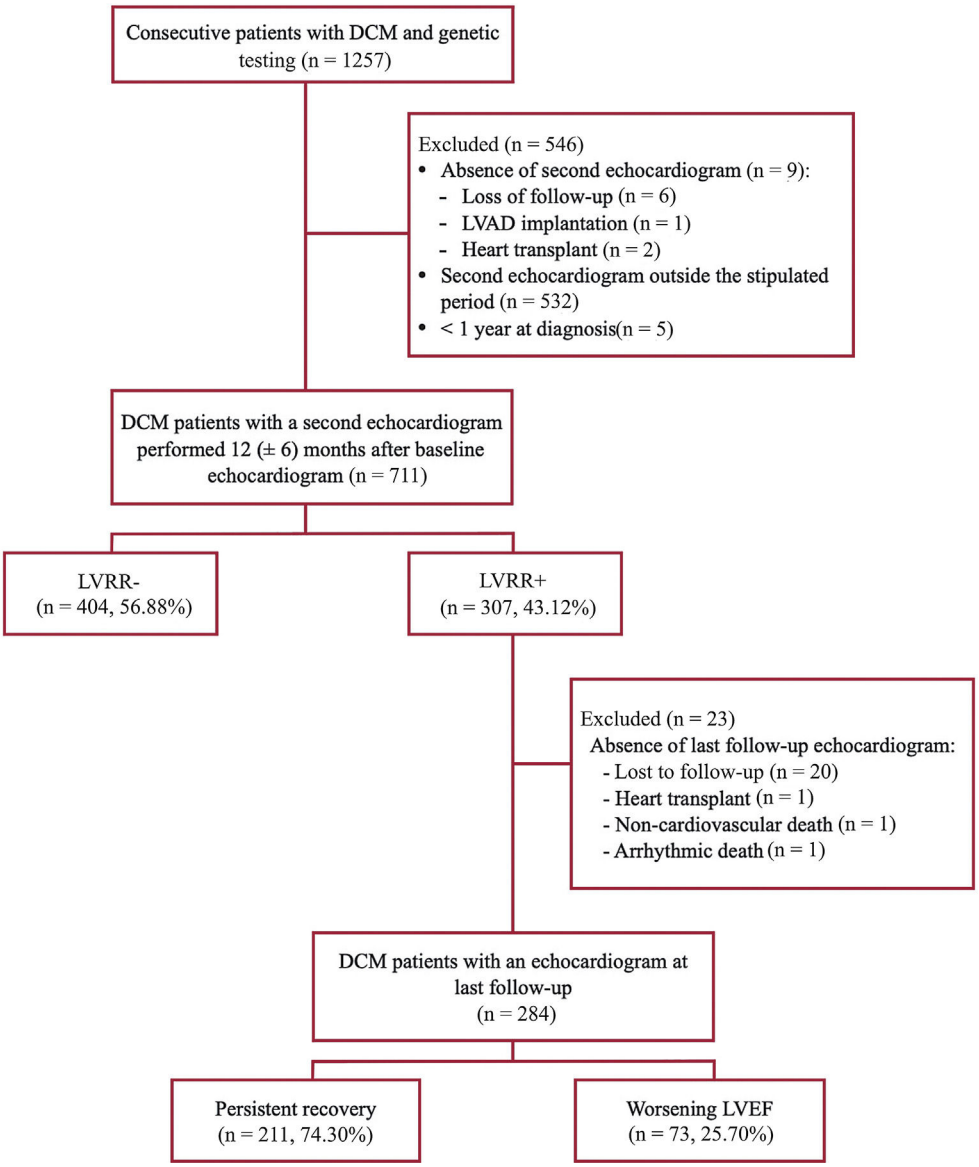

Figure 1. Flow chart of the study. DCM, dilated cardiomyopathy; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling.

therapy was not well established in the inclusion period of our study, and information was not available on all patients.

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. Univariate Cox regression models were used to assess the association of LVRR status at the last follow-up with the clinical objectives (MACE, ESHF, and MVA). Analyses were conducted using Stata Statistics version 15 (StataCorp). A 2-tailed *P* value of < .05 was considered statistically significant.

RESULTS

A total of 711 DCM patients from the 1257 individuals with DCM included in the Spanish genetic DCM study had an echocardiogram performed 12 ± 6 months after initial evaluation and met the inclusion criteria (figure 1). Of them, 618 (86.9%) were unrelated index cases and 93 (13.1%) were relatives.

Demographic, clinical, and imaging baseline characteristics are presented in table 1. Male sex prevailed (67.3%), the median age at diagnosis was 50.8 [40.6-61.6] years, and most patients were in New York Heart Association functional class I or II (63.7%). Median baseline LVEF was 31% [23%-40%].

A total of 312 individuals (43.9%) exhibited 1 or more P/LP variants, while 138 (19.4%) had a variant of unknown significance and 261 (36.7%) had a negative genetic test. Among the 304 participants with 1 P/LP variant, the most frequently involved gene was *TTN* (107, 35.2%), followed by *LMNA* (36, 11.8%), *DSP* (27, 8.9%), *BAG3* (23, 7.6%), *RBM20* (22, 7.2%) and *FLNC* (16, 5.3%), as detailed in table S1.

Regarding medical treatment, at the time of the mid-term echocardiogram, 617 (90.6%) patients were treated with beta-blockers, 645 (90.9%) with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or an angiotensin receptor/neprilysin inhibitor, 413 (61.0%) with mineralocorticoid receptor antagonists, and 81 (3.4%) with sodium-glucose cotransporter type 2 inhibitors (SGLT2i). Medication doses in the overall cohort and

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Table 1
Baseline characteristics of the patients according to left ventricular reverse remodeling at mid-term

Variables	Total (n = 711)	With LVRR (n = 307)	Without LVRR (n = 404)	*P*
Demographics				
Male sex (n = 711)	479 (67.37)	206 (67.10)	273 (67.57)	.894
Age at diagnosis, y (n = 711)	50.84 [40.62-61.60]	51.67 [42.64-63.40]	50.26 [39.62-60.31]	.049
Proband (n = 711)	618 (86.92)	281 (91.53)	337 (83.42)	.001
FH of DCM (n = 711)	362 (50.91)	140 (45.60)	222 (54.95)	.014
FH of SCD first-degree relative (n = 711)	88 (12.38)	32 (10.42)	56 (13.86)	.168
FH of SCD non-first-degree relatives (n = 711)	137 (19.27)	44 (14.33)	93 (23.02)	.004
Skeletal myopathy (n = 711)	28 (3.94)	10 (3.26)	18 (4.46)	.416
Hypertension (n = 711)	221 (31.08)	94 (30.62)	127 (31.44)	.816
Diabetes mellitus (n = 711)	108 (15.19)	48 (15.64)	60 (14.85)	.773
Dyslipidemia (n = 711)	186 (26.16)	79 (25.73)	107 (26.49)	.821
Smoking (n = 706)	291 (41.22)	138 (45.10)	153 (38.25)	.067
NYHA (n = 706)				
I	220 (31.16)	76 (24.84)	144 (36.00)	
II	230 (32.58)	89 (29.08)	141 (35.25)	< .001
III	216 (30.59)	119 (38.89)	97 (24.25)	
IV	40 (5.67)	22 (7.19)	18 (4.50)	
Arrhythmia (SVT, SCD) at diagnosis (n = 706)	29 (4.08)	11 (3.58)	18 (4.46)	.560
HF hospitalization at diagnosis (n = 706)	213 (30.17)	126 (41.04)	87 (21.80)	< .001
Baseline ECG				
Atrial fibrillation (n = 711)	114 (16.03)	44 (14.33)	70 (17.33)	.281
AV block (third degree) (n = 708)	16 (2.26)	6 (1.95)	10 (2.49)	.632
QRS duration, mm (n = 708)	106 [94-134.5]	106 [95-139]	106 [94-134]	.666
LBBB (n = 708)	194 (27.40)	87 (28.34)	107 (26.68)	.625
Abnormal T-wave inversion (n = 489)	165 (33.74)	85 (39.72)	80 (29.09)	.014
Low QRS voltage limb leads (n = 707)	111 (15.70)	46 (14.98)	65 (16.25)	.646
Low QRS voltage precordial leads (n = 707)	38 (5.37)	12 (3.91)	26 (6.50)	.130
Baseline echocardiogram				
LVEF, % (n = 711)	31 [23-40]	27 [20-35]	35 [26.85-43]	< .001
LVEDD, mm (n = 692)	60 [55-66]	61 [56-67]	59 [55-66]	.008
MR moderate/severe (n = 693)	243 (35.06)	123 (40.86)	120 (30.61)	.005
LA, mm (n = 527)	43.01 ± 8.20	43.61 ± 7.13	42.59 ± 8.88	.144
PASP ≥ 50 mmHg (n = 542)	104 (19.19)	51 (21.16)	53 (17.61)	.296
RVSD (any degree) (n = 672)	168 (25.00)	87 (29.59)	81 (21.43)	.015
Treatment at baseline				
Beta-blocker (n = 700)	583 (83.29)	265 (86.32)	318 (80.92)	.057
ACE inhibitor/ARBs or ARNI (n = 711)	629 (88.47)	278 (90.55)	351 (86.88)	.129
ACE inhibitor/ARB (n = 700)	579 (82.71)	246 (80.13)	333 (84.73)	.110
Sacubitril/valsartan (n = 700)	50 (7.14)	32 (10.42)	18 (4.58)	.003
MRA (n = 700)	314 (44.86)	161 (52.44)	153 (38.93)	< .001
iSGLT2 (n = 661)	81 (12.25)	46 (16.14)	35 (9.31)	.008
Treatment at mid-term				
Beta-blocker (n = 681)	617 (90.60)	282 (93.69)	335 (88.16)	.014
ACE inhibitor/ARBs or ARNI (n = 711)	645 (90.72)	289 (94.14)	356 (88.12)	.006
ACE inhibitor/ARB (n = 680)	524 (77.06)	215 (71.67)	309 (81.32)	.003
Sacubitril/valsartan (n = 678)	122 (17.99)	74 (24.67)	48 (12.70)	< .001
MRA (n = 677)	413 (61.00)	199 (66.33)	214 (56.76)	.011
iSGLT2 (n = 566)	91 (15.17)	53 (20.08)	38 (11.31)	.003

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Table 1 *(Continued)*
Baseline characteristics of the patients according to left ventricular reverse remodeling at mid-term

Variables	Total (n = 711)	With LVRR (n = 307)	Without LVRR (n = 404)	*P*
ICD (n = 711)	192 (27.00)	82 (26.71)	110 (27.23)	.878
CRT (n = 711)	67 (9.42)	29 (9.45)	38 (9.41)	.985
Genotype (n = 711)				
Negative	399 (56.12)	186 (60.59)	213 (52.72)	.036
Positive	312 (43.88)	121 (39.41)	191 (47.28)	
Genotype				
Negative	399 (56.76)	186 (60.98)	213 (53.52)	< .001
Cytoskeleton/Z-disk	30 (4.27)	10 (3.28)	20 (5.03)	
Desmosomal	32 (4.55)	5 (1.64)	27 (6.78)	
Nuclear envelope	40 (5.69)	7 (2.30)	33 (8.29)	
Motor sarcomeric	46 (6.54)	14 (4.59)	32 (8.04)	
TTN	107 (15.22)	63 (20.66)	44 (11.06)	
Other genes	49 (6.97)	20 (6.56)	29 (7.29)	

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; FH, family history; iSGLT2, sodium-glucose cotransporter 2 inhibitor; 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; SVT, sustained ventricular tachycardia.
The values are expressed as No. (%), mean ± standard deviation, or median [interquartile range], as appropriate.

according to genotype groups are summarized in table S2 and table S3. Lastly, 301 (42.3%) patients had an ICD and 127 (17.9%) a CRT device at the last follow-up.

Left ventricular reverse remodeling at mid-term

A total of 307 individuals (43.2%) exhibited LVRR at mid-term evaluation (mean time 11.4 ± 3.4 months), 46.6% (n = 186) of patients from the genotype-negative group and 38.8% (n = 121) in the genotype-positive group (*P* = .036). The distribution of genes according to functional gene group and LVRR is compiled in figure S1. Patients with a negative genotype and carriers of a variant in *TTN* showed the highest rate of LVRR (59% and 47%, respectively). In contrast, patients from other genotype groups showed a very low probability of LVRR, particularly in carriers of variants in desmosomal and nuclear envelope genes, where only 16% and 18% of patients achieved LVRR, respectively (figure 2).

Patients with LVRR were older at diagnosis than patients without LVRR (51.7 years [IQR 42.6-63.4 years] vs 50.3 years [IQR 39.6-60.3 years]; *P* = .049), were more likely to be probands (91.5% vs 83.4%; *P* = .001), and had worse New York Heart Association functional class (table 1). In line with the finding of a lower proportion of patients with LVRR among participants with a positive genotype, a family history of DCM or SCD was more frequent in patients without LVRR. Regarding echocardiographic findings, LVEF was lower, LVEDD higher, right ventricular systolic dysfunction, and moderate or severe mitral regurgitation were more prevalent in patients who had LVRR (Table 1).

Clinical and genetic predictors of left ventricular reverse remodeling

Several parameters were associated with LVRR at mid-term in the univariate analysis: *TTN* gene, higher age at diagnosis, proband, higher LVEDD, moderate or severe mitral regurgitation, right ventricular systolic dysfunction, worse New York Heart Association functional class, previous hospitalization due to heart failure, and treatment with mineralocorticoid receptor antagonists and SGLT2i. On the other hand, several genotypes (desmosomal, nuclear envelope, and motor sarcomeric genes) and a positive family history of DCM and SCD were negatively associated with LVRR at mid-term in univariate logistic regression. In the multivariate analysis, previous admission due to heart failure, a lower LVEF, along with either negative or *TTN* genotypes were associated with LVRR. Of note, a genetic variant in *TTN* was the strongest positive predictor for LVRR after adjustment for treatment and other clinical variables (odds ratio [OR], 2.02; 95% confidence interval [95%CI], 1.23-3.30). In contrast, genetic variants in desmosomal (OR, 0.17; 95%CI, 0.05-0.59), nuclear envelope (OR, 0.38; 95%CI, 0.14-0.98), and motor sarcomeric genes (OR, 0.43; 95%CI, 0.21-0.88) remained strongly negatively associated with LVRR in multivariate analysis (table 2). Neurohormonal treatment lost significance after adjusting for the rest of the clinical and genetic variables.

Left ventricular reverse remodeling and prognosis

After a median follow-up since mid-term evaluation of 4.43 years [IQR 2.1-7.5 years], MACE occurred in 156 patients (21.9%), 97 (13.6%) had ESHF events, and 79 (11.1%) had MVA.

Outcomes according to LVRR at mid-term are presented in figure 3 and table S4. MACE occurred in 121 (30.0%) patients among those without LVRR and in 35 (11.4%) patients among those with LVRR. The hazard ratio (HR) for MACE in patients without LVRR was 2.88 (95%CI, 1.92-4.33; *P* < .001) compared with LVRR peers. ESHF occurred in 80 (19.8%) patients in the group without LVRR and in 17 (5.5%) in the group with LVRR (HR, 3.80; 95%CI, 2.25-6.42; *P* < .001). MVA occurred in 60 (14.9%) in the group without LVRR and in 19 (6.2%) in the group with LVRR (HR, 2.60; 95%CI, 1.50-4.50; *P* < .001).

Maintenance of left ventricular reverse remodeling at long-term

Among the 284 patients who exhibited LVRR at mid-term and who underwent long-term evaluation, 73 patients (25.7%) experienced LVEF worsening; 21.6% (n = 37) of genotype-negative and 31.9% (n = 36) in genotype-positive (*P* = .054). Maintenance of LVRR

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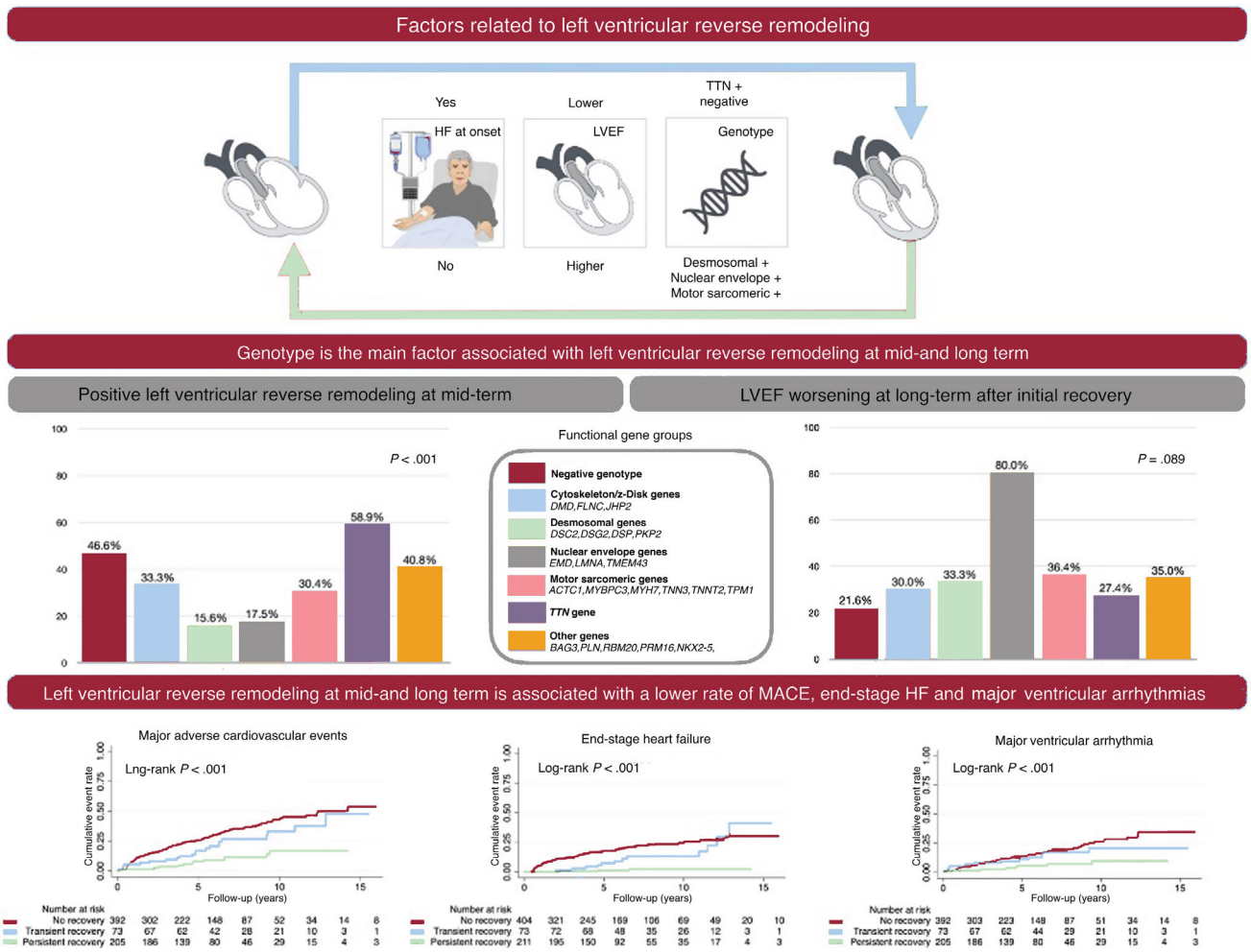

Figure 2. Central illustration. Cumulative event rates for the composite of major adverse cardiovascular events, end-stage heart failure, and major ventricular arrhythmia at the last follow-up according to response to medical treatment. "No recovery" includes patients without LVRR at mid-term; "transient recovery" includes patients with LVRR at mid-term and worsening of LVEF at last-follow-up; "persistent recovery" includes patients with LVRR at mid-term and persistent LVRR at last-follow-up. HF, heart failure; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling.

or deterioration of LV function at long-term according to genotype functional groups is presented in figure S2.

Demographic, clinical, and imaging characteristics are shown in table 3. Patients with LVEF worsening were more often males (78.1% vs 64.5%; $P = .03$) and had a higher LVEF at mid-term (48.0% vs 45.6%; $P = .049$). Other clinical characteristics and echocardiographic parameters were similar between those who maintained LVRR and those who did not. Notably, LVEF decline occurred despite patients remaining on neurohormonal therapy.

Left ventricular reverse remodeling at long-term and prognosis

Outcomes and events according to LVRR persistence at long-term are presented in table S5. After a median follow-up of 4.54 years [IQR 2.80-7.53 years], 33 patients had MACE (11.6%), 16 (5.6%) had ESHF events, and 18 (6.3%) MVA. MACE occurred in 18 (24.7%) patients in the worsening LVEF group and in 15 (7.1%) patients in the persistent LVRR group. The HR for MACE was 2.34 (95%CI, 1.17-4.71; $P = .017$) for patients with LVEF worsening compared with the persistent-LVRR group. ESHF occurred in 13 (17.8%) patients in the worsening LVEF group and 3 (1.4%) patients in the persistent LVRR group (HR, 7.82; 95%CI, 2.20-27.83; $P < .001$). MVA occurred in 9 (12.3%) patients in the worsening LVEF group and 9 (4.3%) patients in the persistent LVRR group (HR, 2.12; 95%CI, 0.79-5.67; $P = .139$) (figure 4, table S6).

DISCUSSION

In this large multicenter study of genotyped patients with DCM, we found that the underlying genotype strongly influenced the chances of achieving LVRR. Furthermore, we found that approximately one quarter of patients with initial LVRR showed subsequent deterioration of LVEF during follow-up and that long-term deterioration also varies according to the underlying genotype. Lastly, we confirm that the absence of LVRR at mid-term and subsequent deterioration at long-term were associated with worse clinical outcomes.

This study constitutes the largest cohort of genotyped DCM patients evaluating treatment response at mid- and long-term reported to date and illustrates the impact of LVRR on prognosis. Our study adds to the available knowledge to consider formulating the indications and timing for ICD implantation in DCM.

Clinical practice guidelines recommend ICD implantation in patients with DCM, symptomatic heart failure, and LVEF ≤ 35%

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Table 2
Left ventricular reverse remodeling-associated variables at univariate and multivariate logistic regression analysis ($P < .05$)

Variables		Univariate analysis		Multivariate analysis	
		OR (95%CI)	*P*	OR (95%CI)	*P*
Genotype	Negative	Ref.	<.001	Ref.	
	Cytoskeleton/Z-disk genes	0.57 (0.26-1.25)	.163	0.60 (0.25-1.45)	.259
	Desmosomal genes	0.21 (0.08-0.56)	.002	0.17 (0.05-0.59)	.005
	Nuclear envelope genes	0.24 (0.10-0.56)	.001	0.38 (0.14-0.98)	.045
	Motor sarcomeric genes	0.50 (0.26-0.97)	.04	0.43 (0.21-0.88)	.021
	TTN gene	1.64 (1.06-2.53)	.025	2.02 (1.23-3.30)	.005
	Other genes	0.79 (0.43-1.44)	.443	0.89 (0.46-1.74)	.735
Proband		2.15 (1.33-3.47)	.001		ns
Age at diagnosis		1.01 (1.00-1.02)	.028		ns
NYHA functional class at first evaluation	I	Ref.	<.001		
	II	1.20 (0.81-1.76)	.361		ns
	III	2.32 (1.58-3.42)	<.001		
	IV	2.32 (1.17-4.58)	.016		
HF hospitalization at diagnosis		2.50 (1.80-3.47)	<.001	1.53 (1.04-2.26)	.032
Abnormal T-wave inversion		1.61 (1.10-2.34)	.014		ni
Baseline LVEF		1.07 (1.05-1.09)*	<.001	1.07 (1.05-1.09)*	<.001
Baseline LVEDD		1.02 (1.00-1.04)	.034		ns
MR moderate/severe		1.57 (1.14-2.15)	.005		ns
RVSD (any degree)		1.54 (1.09-2.19)	.016		ns
MRA		1.73 (1.28-2.34)	<.001		ns
iSGLT2		1.85 (1.16-2.96)	.010		ni

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; DCM, idiopathic dilated cardiomyopathy; FH, family history; HF, heart failure; iSGLT2, sodium-glucose cotransporter 2 inhibitor; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MR, mitral regurgitation; ni, not included; ns, not significant; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RVSD, right ventricular systolic dysfunction; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia..

* LVEF: per point percentage decrease.

after ≥ 3 months of optimal medical treatment.[12,18,19] A 3-month period after optimal medical treatment is required to re-evaluate LVEF and stratify the risk of sudden death. Our study identifies a large subgroup of patients (negative genotype and carriers of *TTN* variants) that are more likely to have favorable remodeling and recover with standard medical therapy at 12 months. Patients with negative genetic testing or harboring *TTN* variants have been reported to have fewer arrhythmic complications. Therefore, in light of our findings, it might be reasonable to wait until 1 year to assess treatment response in patients with these genotypes. In contrast, patients with other genotypes (particularly desmosomal and nuclear envelope genes) exhibited reduced LVRR at mid-term and a greater risk of worsening LVEF at long- term even after an initial recovery, which were both associated with worse outcomes during follow-up. According to these findings, it might be reasonable to behave more aggressively in patients with these genotypes and proceed to ICD implantation without waiting for LVEF response.

Our study shows that LVRR at mid-term is associated with better prognosis. The rate of LVRR among studies is highly variable, ranging from 9% to 52% of patients.[7,11,20–24] Potential explanations for the heterogeneous rates of LVRR reported are the different LVRR definitions used, the time at which LVRR was assessed, the period in which the studies were carried out, and the genetic diversity of the patients studied. In our study, 43% of patients achieved LVRR after 1 year of optimal medical treatment, while a recent Dutch study of 346 patients reported LVRR in 52% of patients.[7] Differences in the number of genotype-positive participants (22% in the Dutch study) and the percentage of patients with more aggressive genotypes (only 12% of genotype positives) might explain the differences found between that study and ours.

Our results indicate that neurohormonal treatment response is largely determined by genotype. DCM patients with a negative genotype and carriers of variants in the *TTN* gene were associated with a high probability of LVRR, while certain genotypes (desmosomal, nuclear envelope, and motor sarcomeric genes) were strong negative predictors for LVRR at mid-term. The lower LVEF and admission for decompensated heart failure at diagnosis were also predictors of positive LVRR, but again all these parameters seemed to be influenced by genotype because the presence of decompensated HF and severe left ventricular dysfunction at diagnosis were more frequent in patients with a negative genotype or who were *TTN* gene carriers. In other genotypes that exhibited a lower rate of LVRR, patients were more likely to be diagnosed earlier after an arrhythmic event or within family screening due to a greater burden of family history of DCM or SCD. In line with our findings, a recent multicenter study by Setti et al.[11] reported that the presence of *TTN* truncating variants was associated with LVRR, whereas the presence of arrhythmogenic gene mutations or a ring-like pattern of late gadolinium enhancement were negatively associated with LVRR at 1 year. These data suggest that integrating genetic and cardiac magnetic resonance imaging findings (including the presence, extent, and localization of late gadolinium enhancement) within a multiparametric framework may aid clinicians in conducting a more personalized risk assessment and in providing reassurance to patients likely to experience LVRR.

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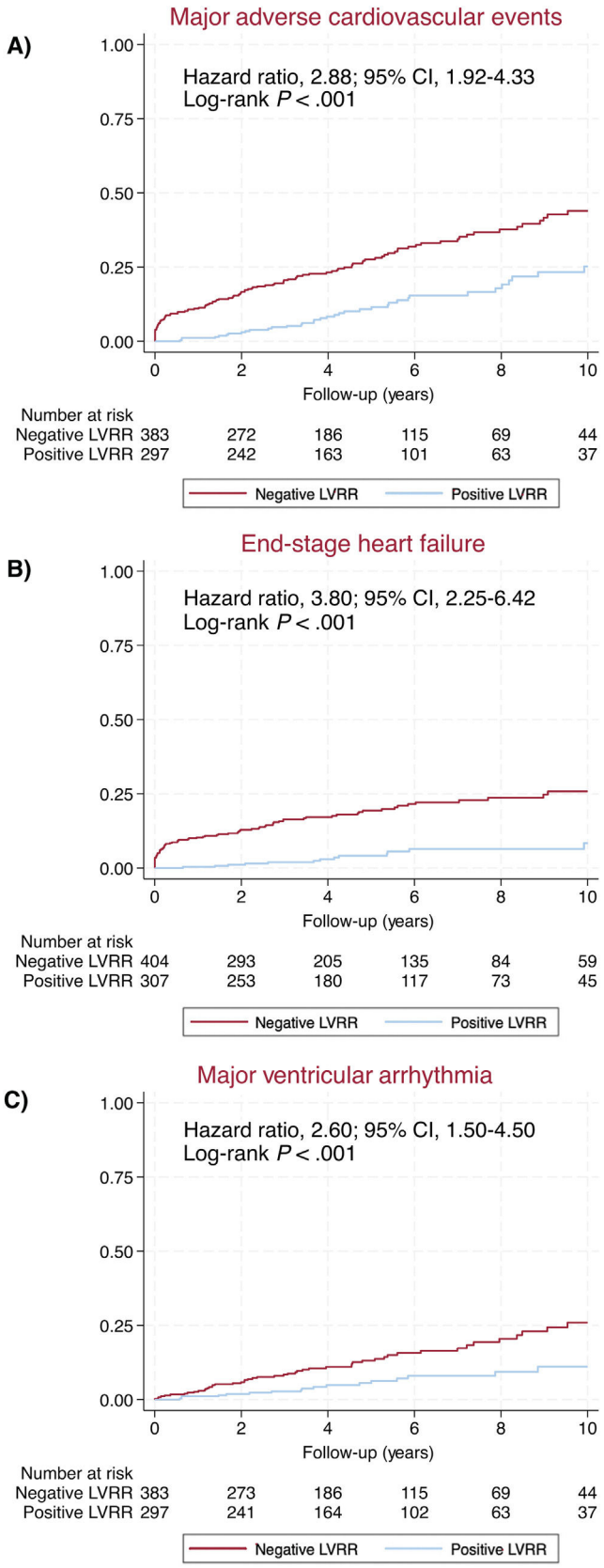

Figure 3. Outcomes in patients with LVRR vs without LVRR. Cumulative event rates for composite (A) major adverse cardiovascular events, (B) end-stage heart failure, and (C) major ventricular arrhythmia at last follow-up. 95%CI, 95% confidence interval; LVRR, left ventricular reverse remodeling.

The most recent guidelines recommend that patients with DCM maintain neurohormonal treatment indefinitely despite LVRR, since patients with recovered LVEF could relapse following treatment withdrawal.[25] Our findings support this recommendation as we found that after an initial recovery, and despite medical treatment, 25% of patients showed worsening LVEF, even among those who normalized LVEF.

So far, information about specific genotypes and treatment response at long-term after initial recovery was only available in patients with variants in *TTN*.[10,13] Our study adds additional information about the impact of genotype on neurohormonal treatment response, showing that patients with variants in nuclear envelope and desmosomal genes have a very low rate of LVRR at mid-term and a high risk of worsening LVEF at long-term. However, as follow-up time increased, these differences became less pronounced, which is likely influenced by the limited number of patients with long-term follow-up. Therefore, larger studies are needed to assess the impact of genotype on treatment response over the very long term and to determine how to integrate this information into a more personalized monitoring scheme for DCM patients, avoiding the current "one- size-fits-all" approach.

Clinical perspectives

Our study adds to the available body of data to consider formulating the indications and timing for ICD implantation in DCM. We identified a subgroup of patients (negative genotype and carriers of *TTN* variants) who exhibit a high rate of LVRR at mid-term and a low rate of clinical events when LVRR occurs. Our data suggest that it may be reasonable to wait longer than the recommended 3-month period to assess treatment response and decide on device implantation in these patients. In contrast, other genetic clusters were associated a very low rate of LVRR at mid-term and with a greater risk of worsening LVEF at long term, even after an initial recovery. In these patients, ICD could be implanted earlier given the high chances of an unfavorable remodeling response. Finally, our study also highlights the need for close follow-up in DCM patients, even after an initial recovery, given the high rate of worsening LVEF and the increased rate of cardiovascular events observed in patients with LVEF deterioration.

Limitations

The limitations of the study include its observational nature and retrospective design. Neurohormonal therapy was initiated and up-titrated according to routine clinical practice. Given the inclusion period of the study, most patients were not receiving SGLT2 inhibitors. Differences in baseline clinical profiles among genotypes may have led to differences in treatment intensity, potentially influencing LVRR outcomes. Main DCM genes were evaluated in all cases, but the genes included in NGS target panels varied between centers and over time, reflecting the evolving knowledge of DCM genetics in recent years. Although this is the largest cohort of genotyped DCM patients with serial echocardiographic evaluations reported to date, the limited number of patients belonging to certain gene groups restricts our ability to reach conclusions about these patients, especially regarding long-term follow-up, where the number of patients is limited. Furthermore, for the purpose of this study, at least two echocardiograms were required throughout follow-up. Therefore, patients who died or required a transplant before the second echocardiogram did not qualify for the study, which may introduce survivor bias. Finally, participating centers were specialized inherited cardiac diseases and heart failure units; therefore, findings might not be extrapolated to other settings.

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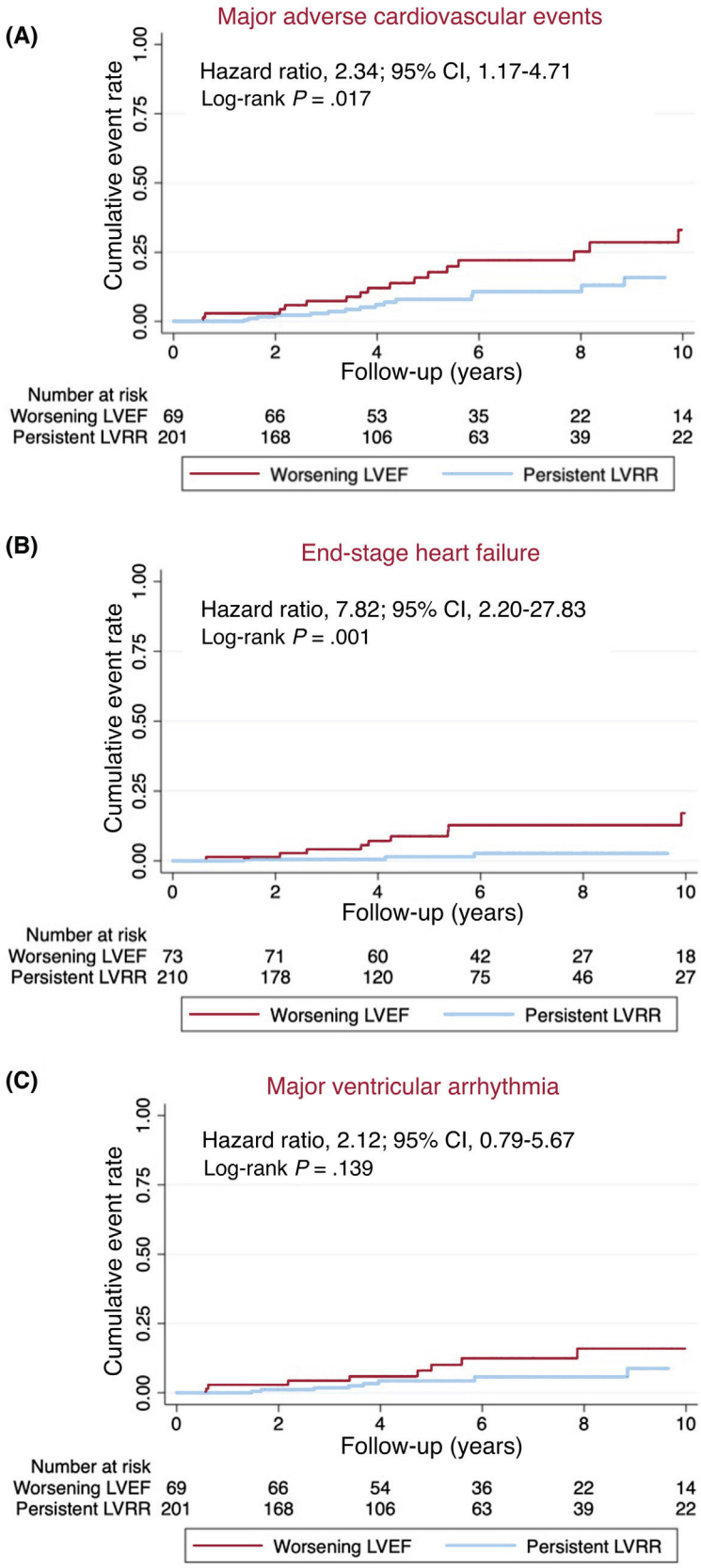

Figure 4. Outcomes in patients with persistent LVRR vs those with worsening LVEF among patients with an initial positive LVRR. Cumulative event rates for (A) major adverse cardiovascular events, (B) end-stage heart failure, and (C) major ventricular arrhythmia at last follow-up. 95%CI, 95% confidence interval; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling.

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Table 3
Characteristics of the patients according to left ventricular reverse remodeling at long-term after initial recovery

Variables	Total (n = 284)	Persistent recovery (n = 211)	Worsening LVEF (n = 73)	*P*
Demographics				
Male sex	193 (67.96)	136 (64.45)	57 (78.08)	.032
Age at diagnosis, y	51.61 [41.96-63.32]	52.28 [43.25-64.13]	50.84 [39.56-60.17]	.234
Proband	258 (90.85)	194 (91.94)	64 (87.67)	.275
FH of DCM	132 (46.48)	99 (46.92)	33 (45.21)	.800
FH of SCD first-degree relative	29 (10.21)	18 (8.53)	11 (15.07)	.112
FH of SCD non-first-degree relatives	41 (14.44)	26 (12.32)	15 (20.55)	.085
FH of skeletal myopathy	2 (0.70)	1 (0.47)	1 (1.37)	.430
Skeletal myopathy	8 (2.82)	5 (2.37)	3 (4.11)	.439
Hypertension	82 (28.87)	66 (31.28)	16 (21.92)	.128
Diabetes mellitus	45 (15.85)	30 (14.22)	15 (20.55)	.202
Dyslipidemia	76 (26.76)	56 (26.54)	20 (27.40)	.887
Smoking	126 (44.52)	88 (41.90)	38 (52.05)	.133
NYHA				
I	68 (24.03)	44 (20.85)	24 (33.33)	
II	82 (28.98)	59 (27.96)	23 (31.94)	.066
III	112 (39.58)	92 (43.60)	20 (27.78)	
IV	21 (7.42)	16 (7.58)	5 (6.94)	
Baseline ECG				
Atrial fibrillation	40 (14.08)	28 (13.27)	12 (16.44)	.502
AV block (third degree)	4 (1.41)	3 (1.42)	1 (1.37)	.974
QRS duration, mm	107 [95-139]	107 [95-140]	108 [97-124]	.801
LBBB	83 (29.23)	65 (30.81)	18 (24.66)	.319
Abnormal T-wave inversion	77 (39.49)	59 (40.97)	18 (35.29)	.476
Low QRS voltage limb leads	42 (14.79)	27 (12.80)	15 (20.55)	.108
Low QRS voltage precordial leads	11 (3.87)	9 (4.27)	2 (2.74)	.560
Baseline echocardiogram				
LVEF, %	27 [20-34.9]	26 [18.8-34]	28 [22-36]	.052
LVEDD, mm	61.81 ± 7.69	62.15 ± 7.84	60.82 ± 7.22	.208
MR moderate/severe	113 (40.50)	87 (41.83)	26 (36.62)	.440
LA, mm	43.75 ± 7.08	43.56 ± 7.13	44.30 ± 6.97	.514
PASP ≥ 50 mmHG	47 (20.80)	33 (19.41)	14 (25.00)	.372
RVSD (any degree)	82 (29.93)	66 (32.35)	16 (22.86)	.134
Mid-term echocardiogram				
LVEF, %	46.17 ± 9.00	45.55 ± 9.28	47.95 ± 7.93	.049
LVEDD, mm	56 [52-61]	56 [51-61]	57 [54-60]	.184
MR moderate/severe	31 (11.57)	23 (11.56)	8 (11.59)	.993
LA, mm	39.93 ± 6.18	39.36 ± 5.82	41.55 ± 6.89	.039
PASP ≥ 50 mmHG	5 (2.19)	4 (2.40)	1 (1.64)	.730
RVSD (any degree)	16 (6.02)	11 (5.56)	5 (7.35)	.591
Medical treatment at last FU				
Beta-blocker	262 (92.25)	196 (92.89)	66 (90.41)	.494
ACE inhibitor/ARBs or ARNI	266 (93.66)	197 (93.36)	69 (94.52)	.727
MRA	196 (69.26)	144 (68.57)	52 (71.23)	.671
iSGLT2	96 (39.02)	63 (35.59)	33 (47.83)	.077
ICD	113 (39.79)	76 (36.02)	37 (50.68)	.027
CRT	46 (16.20)	37 (17.54)	9 (12.33)	.298
Genotype				
Negative	171 (60.21)	134 (63.51)	37 (50.68)	.054
Positive	113 (39.79)	77 (36.49)	36 (49.32)	
Genotype				
Negative	171 (60.64)	134 (64.11)	37 (50.68)	.089
Cytoskeleton/Z-disk	10 (3.55)	7 (3.35)	3 (4.11)	
Desmosomal	3 (1.06)	2 (0.96)	1 (1.37)	
Nuclear Envelope	5 (1.77)	1 (0.48)	4 (5.48)	

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Table 3 *(Continued)*
Characteristics of the patients according to left ventricular reverse remodeling at long-term after initial recovery

Variables	Total (n = 284)	Persistent recovery (n = 211)	Worsening LVEF (n = 73)	*P*
Motor sarcomeric	11 (3.90)	7 (3.35)	4 (5.48)	
TTN	62 (21.99)	45 (21.53)	17 (23.29)	
Other genes	20 (7.09)	13 (6.22)	7 (9.59)	

ACE inhibitor, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; FH, family history; iSGLT2, sodium-glucose cotransporter 2 inhibitors; 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; SVT, sustained ventricular tachycardia.
The values are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

CONCLUSIONS

Patients with DCM and a positive genotype have a lower rate of LVRR at mid-term and are at greater risk of worsening LVEF in the long term after an initial recovery, with the exception of the *TTN* variant. Genotype is the main factor associated with LVRR in DCM. A significant number of individuals with initial LVRR show subsequent deterioration of LVEF, which is associated with worse clinical outcomes.

FUNDING

This work was supported by grants from Instituto de Salud Carlos III "PI20/0320" (co-funded by the European Regional Development Fund/European Social Fund "A way to make Europe"/"Investing in your future"). The CNIC is supported by the ISCIII, MCIN, the Pro-CNIC Foundation, and the Severo Ochoa Centers of Excellence program (CEX2020-001041-S).

ETHICAL CONSIDERATIONS

The study was approved by the *Hospital Universitario Puerta de Hierro* ethics committee, which waived the requirement for informed consent. The study conformed to the principles of the Declaration of Helsinki. The authors from each participating center guarantee the integrity of the data. In accordance with the SAGER guidelines, sex and gender are not relevant to the results of the study.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this manuscript.

AUTHORS CONTRIBUTIONS

Project conception and leadership: N. Mora-Ayestarán, P. García-Pavía, F. Domínguez. Data collection: N. Mora-Ayestarán, M.A. Espinosa-Castro, M. Navarro-Peñalver, E. Villacorta, M.G. Crespo-Leiro, V. Climent-Payá, G. Lacuey-Lecumberri, M.L. Peña-Peña, F.J. Bermúdez-Jiménez, J.M. García-Pinilla, M.V. Mogollón-Jiménez, J. Limeres-Freire, A. García-Álvarez, A. Bayés-Genís, J. Palomino-Doza, C. Tirón, T. Ripoll-Vera, J. López, M. Brion, S. Vilches-Soria, M. Sabater-Molina, B. García-Berrocal, J.M. Larrañaga-Moreira, M.I. García-Álvarez, M.T. Basurte-Elorz, H. Llamas-Gómez, I. Méndez-Fernández, I.P. Garrido-Bravo, E. González-López, M. Gallego-Delgado, R. Barriales-Villa. Data interpretation and analysis: N. Mora-Ayestarán, P. García-Pavía, J.P. Ochoa, and F. Domínguez interpreted and analyzed the clinical and genetic data. Manuscript preparation: N. Mora-Ayestarán, P. García-Pavía, J.P. Ochoa, and F. Domínguez drafted the manuscript with input from co-authors: M.A. Espinosa-Castro, M. Navarro-Peñalver, E. Villacorta, M.G. Crespo-Leiro, V. Climent-Payá, G. Lacuey-Lecumberri, M.L. Peña-Peña, F.J. Bermúdez-Jiménez, J.M. García-Pinilla, M.V. Mogollón-Jiménez, J. Limeres-Freire, A. García-Álvarez, A. Bayés-Genís, J. Palomino-Doza, C. Tirón, T. Ripoll-Vera, J. López, M. Brion, S. Vilches-Soria, M. Sabater-Molina, B. García-Berrocal, J.M. Larrañaga-Moreira, M.I. García-Álvarez, M.T. Basurte-Elorz, H. Llamas-Gómez, I. Méndez-Fernández, I.P. Garrido-Bravo, E. González-López, M. Gallego-Delgado, R. Barriales-Villa, E. Lara-Pezzi. All authors substantially contributed to the manuscript.

CONFLICTS OF INTEREST

P. García-Pavía is an associate editor of *Revista Española de Cardiología*; the journal's editorial procedures to ensure impartial processing of the manuscript were followed. P. García-Pavía and F. Domínguez are funded by the Pathfinder Cardiogenomics Programme of the European Innovation Council of the European Union (DCM-NEXT project; grant 101115416). The remaining authors report no relationships relevant to the contents of this paper to disclose. The *Hospital Universitario Puerta de Hierro, Hospital Clínic, Hospital Vall d'Hebron, Hospital Virgen del Rocío, Hospital Universitario Gregorio Marañón*, and *Hospital Universitario Virgen de la Arrixaca* are members of the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart).

WHAT IS KNOWN ABOUT THE TOPIC?

- Patients with nonischemic dilated cardiomyopathy who respond favorably to medical therapy have a better prognosis. In contrast, a positive genetic test for variants associated with dilated cardiomyopathy is linked to a higher incidence of adverse clinical events during follow-up.

WHAT DOES THIS STUDY ADD?

- A negative genotype and TTN variants are associated with a higher likelihood of left ventricular reverse remodeling, whereas other positive genotypes are associated with a lower probability of remodeling. Despite an initial favorable response, a substantial proportion of patients subsequently experience recurrent deterioration of left ventricular ejection fraction, which is associated with an increased risk of cardiovascular events.

Please cite this article in press as: Mora-Ayestarán N, et al. Association of genotype with treatment response and prognosis in dilated cardiomyopathy. *Rev Esp Cardiol.* 2025. https://doi.org/10.1016/j.rec.2025.10.002

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2025.10.002.

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Please cite this article in press as: Mora-Ayestarán N, et al. Association of genotype with treatment response and prognosis in dilated cardiomyopathy. *Rev Esp Cardiol.* 2025. https://doi.org/10.1016/j.rec.2025.10.002