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Association of Genetic Variants With Outcomes in Patients With Nonischemic Dilated Cardiomyopathy

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ABSTRACT

BACKGROUND The clinical relevance of genetic variants in nonischemic dilated cardiomyopathy (DCM) is unsettled.

OBJECTIVES The study sought to assess the prognostic impact of disease-causing genetic variants in DCM.

METHODS Baseline and longitudinal clinical data from 1,005 genotyped DCM probands were retrospectively collected at 20 centers. A total of 372 (37%) patients had pathogenic or likely pathogenic variants (genotype positive) and 633 (63%) were genotype negative. The primary endpoint was a composite of major adverse cardiovascular events. Secondary endpoints were end-stage heart failure (ESHF), malignant ventricular arrhythmia (MVA), and left ventricular reverse remodeling (LVRR).

RESULTS After a median follow-up of 4.04 years (interquartile range: 1.70-7.50 years), the primary endpoint had occurred in 118 (31.7%) patients in the genotype-positive group and in 125 (19.8%) patients in the genotype-negative group (hazard ratio [HR]: 1.51; 95% confidence interval [CI]: 1.17-1.94; $P = 0.001$). ESHF occurred in 60 (16.1%) genotype-positive patients and in 55 (8.7%) genotype-negative patients (HR: 1.67; 95% CI: 1.16-2.41; $P = 0.006$). MVA occurred in 73 (19.6%) genotype-positive patients and in 77 (12.2%) genotype-negative patients (HR: 1.50; 95% CI: 1.09-2.07; $P = 0.013$). LVRR occurred in 39.6% in the genotype-positive group and in 46.2% in the genotype-negative group ($P = 0.047$). Among individuals with baseline left ventricular ejection fraction ≤35%, genotype-positive patients exhibited more major adverse cardiovascular events, ESHF, and MVA than their genotype-negative peers (all $P < 0.02$). LVRR and clinical outcomes varied depending on the underlying affected gene.

CONCLUSIONS In this study, DCM patients with pathogenic or likely pathogenic variants had worse prognosis than genotype-negative individuals. Clinical course differed depending on the underlying affected gene.
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Nonischemic dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and systolic dysfunction that cannot be attributed to abnormal loading conditions or to coronary artery disease. It has an estimated population prevalence of 1:250 to 1:2,500 and is the most frequent cause of heart failure in the young and the leading cause of heart transplantation worldwide. DCM constitutes a common substrate for ventricular arrhythmias and is associated with a higher risk of sudden cardiac death (SCD) (1,2).

In up to 40%-50% 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 DCM. Indeed, there is growing evidence that the clinical course depends on the underlying affected gene (2-5).

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With the exception of DCM caused by genetic variants in *TTN* and *LMNA* genes (6-9), our understanding of the natural history of genetic DCM is poor. Comprehensive information on the clinical impact of genetic findings in DCM is limited, and data from large cohorts are not available (2). Accordingly, the present study sought to assess the clinical impact of genotype findings on prognosis in a large multicenter cohort of patients with nonischemic DCM.

METHODS

STUDY POPULATION. This was a multicenter, retrospective, observational, and longitudinal study of consecutive genetically evaluated probands with DCM recruited from inherited cardiac diseases and heart failure units at 20 Spanish hospitals between 2015 and 2020.

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 cause (10). Only patients aged >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.

Most of the centers had inherited cardiac diseases programs and followed the recommendations of the Spanish Society of Cardiology (11). On the first contact, familial data were obtained after a structured interview and a family pedigree was drawn. Clinical screening and cascade genetic screening (if

ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

ESHF = end-stage heart failure

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

MACE = major adverse cardiovascular event

MVA = malignant ventricular arrhythmia

NGS = next-generation sequencing

SCD = sudden cardiac death

TTE = transthoracic echocardiogram

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pathogenic or likely pathogenic variant were identified) were offered to relatives.

Although the study primary cohort included only unrelated DCM probands, consecutive relatives with DCM (n = 156) who harbored a pathogenic or likely pathogenic genetic variant previously identified by NGS panels of >50 genes in a DCM proband were added to the cohort in order to expand the genotype-positive group and analyze clinical outcomes according to genotype and LVEF. Demographics, symptoms, 12-lead electrocardiogram, and transthoracic echocardiogram (TTE) data at first and last evaluation at participating centers were extracted from clinical records using uniform methodology. DCM was defined as familial if 1 or more relatives (in addition to the proband) had DCM during life or at postmortem examination; sporadic case was used indistinctly as nonfamilial DCM, indicating that there was no family history of DCM and that 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 a SCD or a heart failure death with a previous diagnosis of DCM.

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 center 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 a cardiologist expert in cardiovascular genetics (J.P.O.) using modified criteria of the American College of Medical Genetics (12), as described in the Supplemental Methods. A variant was considered disease causing if it affected a DCM-related gene and was classified as pathogenic or likely pathogenic. Patients harboring pathogenic or likely pathogenic variants were considered genotype positive, and patients harboring unknown significance, likely benign, or benign variants were considered genotype negative (Supplemental Figure 1).

The variants' frequencies in the general population were extracted from the gnomAD database v2.1.1 (13). We also added the information of more than 5,254 index cases with no evidence of structural cardiac disease (channelopathies and aortic diseases) sequenced by NGS in the Health in Code Molecular Genetics Laboratory (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.

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 (14). Because of its specific characteristics of frequency in DCM, *TTN* was considered as a separate group. Functional gene groups included the following: 1) structural cytoskeleton/Z-disk; 2) desmosomal; 3) nuclear envelope; 4) motor sarcomeric; 5) *TTN*; and 6) other genes. Individuals with more than 1 pathogenic or likely pathogenic variant were excluded from the functional gene group analysis to maintain a conservative approach.

OUTCOMES. The primary endpoint was a composite of major adverse cardiovascular events (MACE), which included end-stage heart failure (ESHF), major ventricular arrhythmias (MVAs), and fatal and nonfatal stroke. Secondary endpoints were ESHF, MVA, and left ventricular reverse remodeling (LVRR). ESHF included ventricular assist device implantation for refractory heart failure, heart transplant, and ESHF-related mortality. MVA included SCD, aborted SCD, sustained ventricular tachycardia, and appropriate implantable cardioverter-defibrillator (ICD) interventions. LVRR was defined as either left ventricular normalization (LVEF improvement to ≥50% with a ≥5% LVEF increment on TTE at the last follow-up) or an absolute increase in LVEF by ≥10% on TTE at the last follow-up from initial TTE at baseline, as described (6,15,16).

All patients had planned reviews every 6 to 12 months or more frequently if clinically indicated. The follow-up for each patient was calculated from the date of their first evaluation at a participating center, to the occurrence of a study endpoint, death from another cause, or the date of their most recent evaluation.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± 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 2 groups. Noncontinuous categorical variables are expressed as counts (percentages) and were compared using the chi-square or Fisher 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

TABLE 1 Characteristics of the Patients According to Genetic Results (n = 1,005)

	Total (N = 1,005)	Genotype Positive (n = 372)	Genotype Negative (n = 633)	*P* Value
Demographics				
Male	688 (68.46)	248 (66.67)	440 (69.51)	0.349
Age at diagnosis, y	51.0 (42.0-61.0)	50.0 (39.5-58.0)	52.0 (43.0-62.0)	<0.001
Age at initial evaluation, y	53.0 (44.0-62.0)	52.0 (42.0-61.0)	54.0 (45.0-64.0)	0.006
Follow-up, y	4.04 (1.70-7.50)	3.96 (2.00-7.10)	4.15 (1.60-7.70)	0.728
FH of DCM	478 (47.56)	226 (60.75)	252 (39.81)	<0.001
FH of SCD first-degree relative	123 (12.24)	61 (16.40)	62 (9.79)	0.002
FH of SCD non-first-degree relatives	188 (18.71)	86 (23.12)	102 (16.11)	0.006
FH of skeletal myopathy	24 (2.39)	13 (3.49)	11 (1.74)	0.078
Skeletal myopathy[a]	35 (3.48)	22 (5.91)	13 (2.05)	0.001
Previous SCD	17 (1.69)	4 (1.08)	13 (2.05)	0.245
NYHA functional class III-IV at first evaluation	358 (35.62)	146 (39.25)	212 (33.49)	0.066
NYHA functional class at first evaluation				0.223
I	306 (30.45)	113 (30.38)	193 (30.49)	
II	341 (33.93)	113 (30.38)	228 (36.02)	
III	304 (30.25)	124 (33.33)	180 (28.44)	
IV	54 (5.37)	22 (5.91)	32 (5.06)	
Baseline ECG				
Atrial fibrillation	116 (11.58)	42 (11.32)	74 (11.73)	0.846
AV block (third degree)	24 (2.39)	12 (3.23)	12 (1.90)	0.182
QRS duration, mm	117.84 ± 29.22	109.22 ± 26.76	122.91 ± 29.44	<0.001
LBBB	331 (33.03)	60 (16.17)	271 (42.95)	<0.001
Abnormal T-wave inversion	364 (36.33)	132 (35.58)	232 (36.77)	0.706
Low QRS voltage limb leads	130 (12.97)	87 (23.45)	43 (6.81)	<0.001
Low QRS voltage precordial leads	45 (4.49)	29 (7.82)	16 (2.54)	<0.001
Baseline echocardiogram				
LVEF, %	31.98 ± 10.46	32.17 ± 10.39	31.87 ± 10.51	0.713
LVEF ≤35%	636 (63.28)	233 (62.63)	403 (63.67)	0.743
LVEDD, mm	61.37 ± 8.04	61.05 ± 7.61	61.56 ± 8.28	0.604
MR moderate/severe	339 (34.98)	132 (36.87)	207 (33.88)	0.346
RVSD (any degree)	208 (23.01)	88 (26.91)	120 (20.80)	0.036
Drug treatment at initial evaluation				
β-blockers	829 (83.57)	306 (83.38)	523 (83.68)	0.902
ACE inhibitors/ARBs	864 (87.10)	316 (86.10)	548 (87.68)	0.475
Sacubitril/valsartan	34 (3.43)	14 (3.81)	20 (3.20)	0.607
ARA	447 (45.06)	185 (50.41)	262 (41.92)	0.009
Treatment at last evaluation				
β-blocker	923 (93.04)	341 (92.92)	582 (93.12)	0.903
ACE inhibitors/ARBs	661 (66.63)	237 (64.58)	424 (67.84)	0.293
Sacubitril/valsartan	265 (26.71)	108 (29.43)	157 (25.12)	0.139
ARA	671 (67.64)	263 (71.66)	408 (65.28)	0.038
ICD	425 (42.29)	189 (50.81)	236 (37.28)	<0.001
CRT	167 (16.62)	43 (11.56)	124 (19.59)	0.001

Values are n (%), median (interquartile range), or mean ± SD. [a]Distribution of genotypes available in Supplemental Table 2.

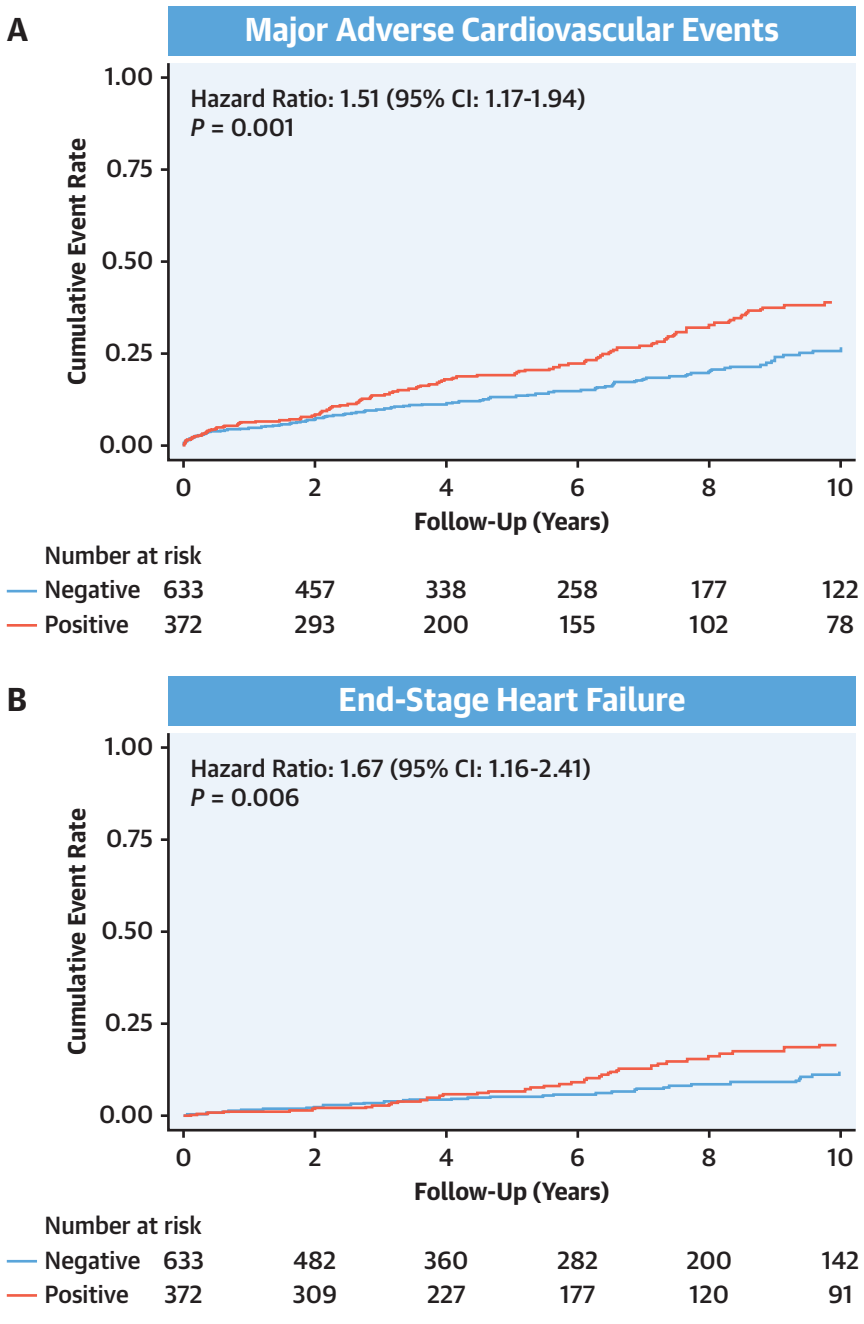
ACE = angiotensin-converting enzyme; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; AV = atrioventricular; CRT = cardiac resynchronization therapy; DCM = idiopathic dilated cardiomyopathy; FH = family history; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; RVSD = right ventricular systolic dysfunction; SCD = sudden cardiac death.

primary and secondary endpoints, a univariate Cox regression model (for MACE, ESHF, and MVA) and a logistic regression analysis (for LVRR) were applied. Analyses were conducted using Stata Statistics version 16 (StataCorp). Two-tailed *P* values of 0.05 or less defined statistical significance.

RESULTS

A total of 1,005 probands met inclusion criteria. Genetic testing was positive in 372 (37.0%) patients; 8 (0.8%) of these index cases harbored 2 disease-causing variants. A complete list of disease-causing variants

FIGURE 1 **Outcomes in Genotype-Positive Versus Genotype-Negative Dilated Cardiomyopathy Index Patients (n = 1,005)**

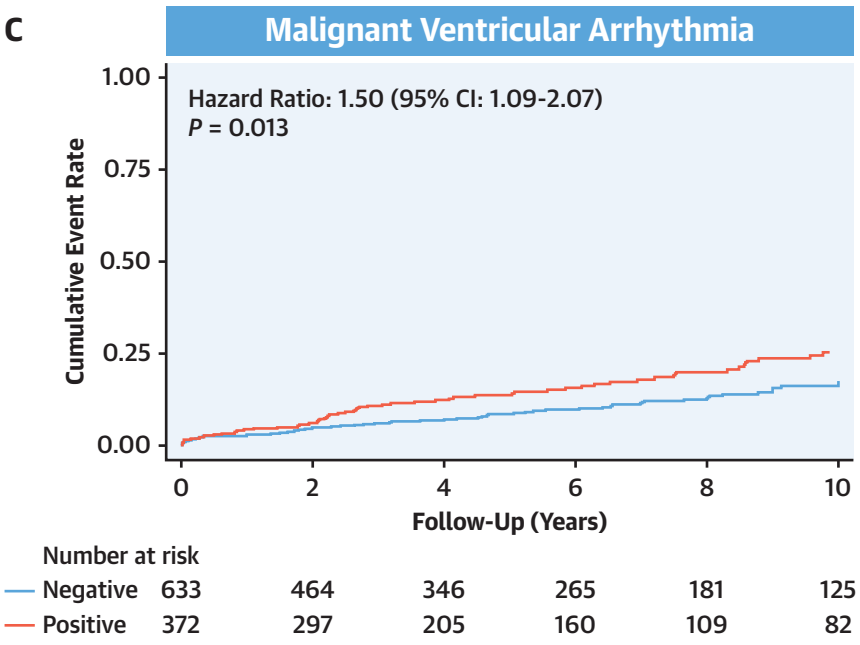


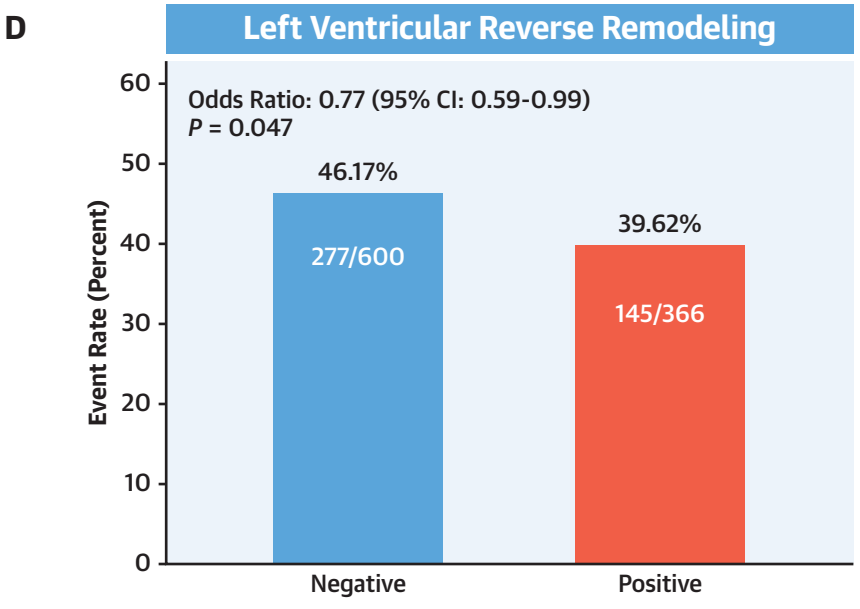
Cumulative incidence for composite **(A)** major adverse cardiovascular events, **(B)** end-stage heart failure, **(C)** malignant ventricular arrhythmia, and **(D)** left ventricular reverse remodeling rate at last follow-up in genotype-positive versus genotype-negative dilated cardiomyopathy index patients. CI = confidence interval.

Continued on the next page

can be found in the Supplemental Appendix. A variant of unknown significance was detected in 244 (24.3%) patients, whereas genetic study failed to identify any relevant variant in 389 (38.7%) patients (Supplemental Figures 2 and 3). The presence of a positive genetic test in index cases was higher in individuals with familial DCM (47.3%, n = 226 of 478) than in sporadic cases (27.7%, n = 146 of 527) ($P < 0.001$).

FIGURE 1 Continued





CHARACTERISTICS OF THE PROBANDS. Characteristics of the patients are presented in **Table 1.** Male sex prevailed (68.5%); median age at diagnosis was 51.0 years (IQR: 42.0-61.0 years), and most patients were in New York Heart Association functional class I or II (64.4%) at baseline. Mean baseline LVEF was 32.0 ± 10.5%, and 63.3% of patients had an LVEF ≤35%. The prevalence of atrial fibrillation was 11.6%; left bundle branch block was present in 33.0% of patients and a third-degree atrioventricular block was present in 2.4%.

Regarding medical treatment, 83.6% of the patients at baseline were treated with β-blockers and 87.1% with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. At last follow-up, 93.0% of patients were receiving β-blockers, 66.6% angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 26.7% sacubitril/

TABLE 2 Outcomes and Events According to Genetic Results (n = 1,005)

Clinical Events	Total (N = 1,005)	Genotype Positive (n = 372)	Genotype Negative (n = 633)	*P* Value
Atrial fibrillation	287 (28.56)	125 (33.60)	162 (25.59)	0.007
Stroke	30 (2.99)	12 (3.23)	18 (2.84)	0.731
Appropriate ICD therapy	93 (9.25)	42 (11.29)	51 (8.06)	0.088
Aborted SCD	31 (3.08)	13 (3.49)	18 (2.84)	0.564
Heart failure hospitalization	338 (33.63)	140 (37.63)	198 (31.28)	0.040
Heart transplant	87 (8.66)	47 (12.63)	40 (6.32)	0.001
LVAD implantation	19 (1.89)	10 (2.69)	9 (1.42)	0.155
All-cause mortality	68 (6.77)	34 (9.14)	34 (5.37)	0.022
HF-related mortality	32 (3.18)	17 (4.57)	15 (2.37)	0.055
MVA-related mortality	14 (1.39)	9 (2.42)	5 (0.79)	0.033
Composite MACE	243 (24.18)	118 (31.72)	125 (19.75)	<0.001
Composite ESHF	115 (11.44)	60 (16.13)	55 (8.69)	<0.001
Composite MVA	150 (14.93)	73 (19.62)	77 (12.16)	0.001
Left ventricular reverse remodeling	422 (43.69)	145 (39.62)	277 (46.17)	0.047

Values are n (%).

ESHF = end-stage heart failure; HF = heart failure; LVAD = left ventricular assist device; MACE = major adverse cardiovascular events; MVA = malignant ventricular arrhythmia; other abbreviations as in Table 1.

valsartan, and 67.6% aldosterone-receptor antagonists. In relation to device therapy, 425 (42.3%) patients had an ICD and 167 (16.6%) received cardiac resynchronization therapy.

Genotype-positive patients were significantly younger at diagnosis than genotype-negative patients (50.0 years [IQR: 39.5-58.0 years] vs 52.0 years [IQR: 43.0-62.0 years]; $P < 0.001$) and were more likely to have a family history of SCD (23.1% vs 16.1%; $P = 0.006$). Baseline echocardiographic parameters were similar between groups, with no difference in LVEF or the proportion of patients with LVEF ≤35%.

Among the 363 index cases with 1 pathogenic or likely pathogenic variant, the most frequently involved genes were *TTN*, identified in 141 (38.7%) individuals, followed by *LMNA* (n = 31 [8.5%]), *DSP* (n = 31 [8.5%]), *BAG3* (n = 24 [6.6%]), *FLNC* (n = 21 [5.8%]), *RBM20* (n = 20 [5.5%]), and *MYH7* (n = 17 [4.7%]). The distribution of genes according to the functional gene group in probands with a unique pathogenic or likely pathogenic variant and their clinical characteristics are listed in Supplemental Tables 1 to 3.

Characteristics of patients did not differ between functional gene groups, except for a trend toward a family history of SCD and skeletal myopathy in the nuclear envelope group. Atrial fibrillation, left bundle branch block, and complete atrioventricular block were also more prevalent in this group (Supplemental Table 4).

OUTCOMES IN PROBANDS. After a median follow-up of 4.04 years (IQR: 1.70-7.50 years), MACE occurred in 243 patients (24.2%), 115 (11.4%) patients had ESHF events, and 150 (14.9%) patients had MVA. Clinical outcomes are presented in Figure 1 and Table 2. MACE occurred in 118 (31.7%) patients in the genotype-positive group and in 125 (19.8%) patients in the genotype-negative group. The hazard ratio (HR) for MACE was 1.51 (95% confidence interval [CI]: 1.17-1.94; $P = 0.001$) for genotype-positive patients compared with the genotype-negative patients. ESHF occurred in 60 (16.1%) patients in the genotype-positive group and in 55 (8.7%) patients in the genotype-negative group (HR: 1.67; 95% CI: 1.16-2.41; $P = 0.006$). MVA occurred in 73 (19.6%) patients in the genotype-positive group and in 77 (12.1%) patients in the genotype-negative (HR: 1.50; 95% CI: 1.09-2.07; $P = 0.013$). LVRR occurred in 422 (43.7%) of the 966 probands with serial echocardiograms suitable for the analysis (median time between baseline and last TTE of 3.93 years [IQR: 1.78-7.29 years]). LVRR occurred more frequently in genotype-negative patients than in genotype-positive patients (46.2% vs 39.6%; $P = 0.047$) (Figure 1D and Supplemental Table 5).

Outcomes differed in genotype-positive patients according to the underlying affected functional gene group (Figure 2 and Supplemental Table 6). The worst cumulative incidence of MACE was observed in the nuclear envelope gene group. Patients from this functional gene group also exhibited higher ESHF and MVA than did patients in the remaining functional groups ($P < 0.001$). The desmosomal and cytoskeleton/Z-disk gene groups exhibited a lower risk of MACE and MVA than the nuclear envelope group but higher risk than the other functional gene groups.

Differences were also noted in LVRR between the functional gene groups (Figure 2D). The *TTN* group had the highest rate of LVRR (53.2%), and the worst response was observed in the desmosomal genes group (11.1%). LVRR of the nuclear envelope, sarcomeric, and cytoskeleton/Z-disk groups was 25.0%, 28.3%, and 42.5%, respectively. When compared with the genotype-negative group, the LVRR rate was lower in the desmosomal, nuclear envelope, and sarcomeric functional groups (all $P < 0.001$).

CHARACTERISTICS OF RELATIVES WITH DCM. A total of 156 genotype-positive relatives with DCM were identified during cascade screening. Compared with probands, relatives were diagnosed younger (43.5 years [IQR: 31.0-57.0 years] vs 51.0 years [IQR: 42.0-61.0 years]; $P < 0.001$) and exhibited a higher LVEF (40.6 ± 9.7% vs 32.0 ± 10.5%) and lower LVEDD (57.0 ± 6.4 vs 61.4 ± 8.0) at initial evaluation (Supplemental Table 7). Not unexpectedly, relatives

had a higher proportion of asymptomatic patients (65.4% vs 30.5%) with a lower proportion of patients with a LVEF ≤35% (24.4% vs 63.3%) (all $P < 0.001$).

Although relatives exhibited a milder DCM phenotype, there were no differences in the composite outcomes of MACE, ESHF, and MVA between index cases and relatives, and LVRR was more frequent in probands than in relatives (43.7% vs 25.0%; $P < 0.001$), supporting also that genotype-positive individuals have worse prognosis than genotype-negative patients, as all relatives included in the analysis were genotype-positive versus only 37% of probands.

Clinical outcomes in the overall cohort and classification by functional gene groups after expansion of the genotype-positive DCM group by the incorporation of relatives provided similar findings to the proband cohort, with increased MACE, ESHF, and MVA and reduced LVRR in genotype-positive DCM and varied clinical course depending on the underlying affected gene (**Figure 3,** Supplemental Figure 4).

EVENTS ACCORDING TO THE PRESENCE OF SEVERE SYSTOLIC CARDIAC DYSFUNCTION. Outcomes in the whole cohort of patients with LVEF ≤35% and >35% are shown in **Figure 4**. Genotype-positive patients with baseline LVEF ≤35% had a higher incidence of MACE (HR: 1.62; 95% CI: 1.22-2.14; $P = 0.001$), ESHF (HR: 1.68; 95% CI: 1.13-2.48; $P = 0.010$), and MVA (HR: 1.58; 95% CI: 1.09-2.28; $P = 0.015$) than did genotype-negative patients with LVEF ≤35%. By contrast, outcomes in genotype-positive and genotype-negative patients with LVEF >35% were not statistically different.

DISCUSSION

In this large multicenter study of genotyped patients with DCM, we found that those with pathogenic or likely pathogenic variants had a worse clinical outcome than their genotype-negative peers. We also found that genetic testing identifies patients at higher risk of MVA and ESHF when LVEF is ≤35%, and that clinical course varies depending on the affected gene (**Central Illustration**).

This study constitutes the largest cohort of genotyped patients with DCM and clinical outcomes data reported to date and illustrates the clinical utility of genetic testing to identify individuals at higher risk of adverse cardiovascular events, namely ESHF and SCD. Pathogenic or likely pathogenic genetic variants were identified in 37.0% of index patients in the cohort, confirming the significant genetic yield in DCM achieved by NGS. The proportion of probands with familial DCM and the diagnostic yield of genetic testing observed in our cohort was relatively high, likely reflecting that the majority of the participant centers had specific inherited cardiac disease programs. Nevertheless, the diagnostic yield and distribution of genes was in line with other recent cohorts from inherited cardiac diseases centers, with *TTN* being the most frequently affected gene (17,18).

Although worse outcomes of genetically caused DCM had been suggested previously (19), this is the first study demonstrating that carrying a DCM mutation is associated with higher risk for clinical endpoints (both arrhythmic and ESHF) compared with genotype-negative patients.

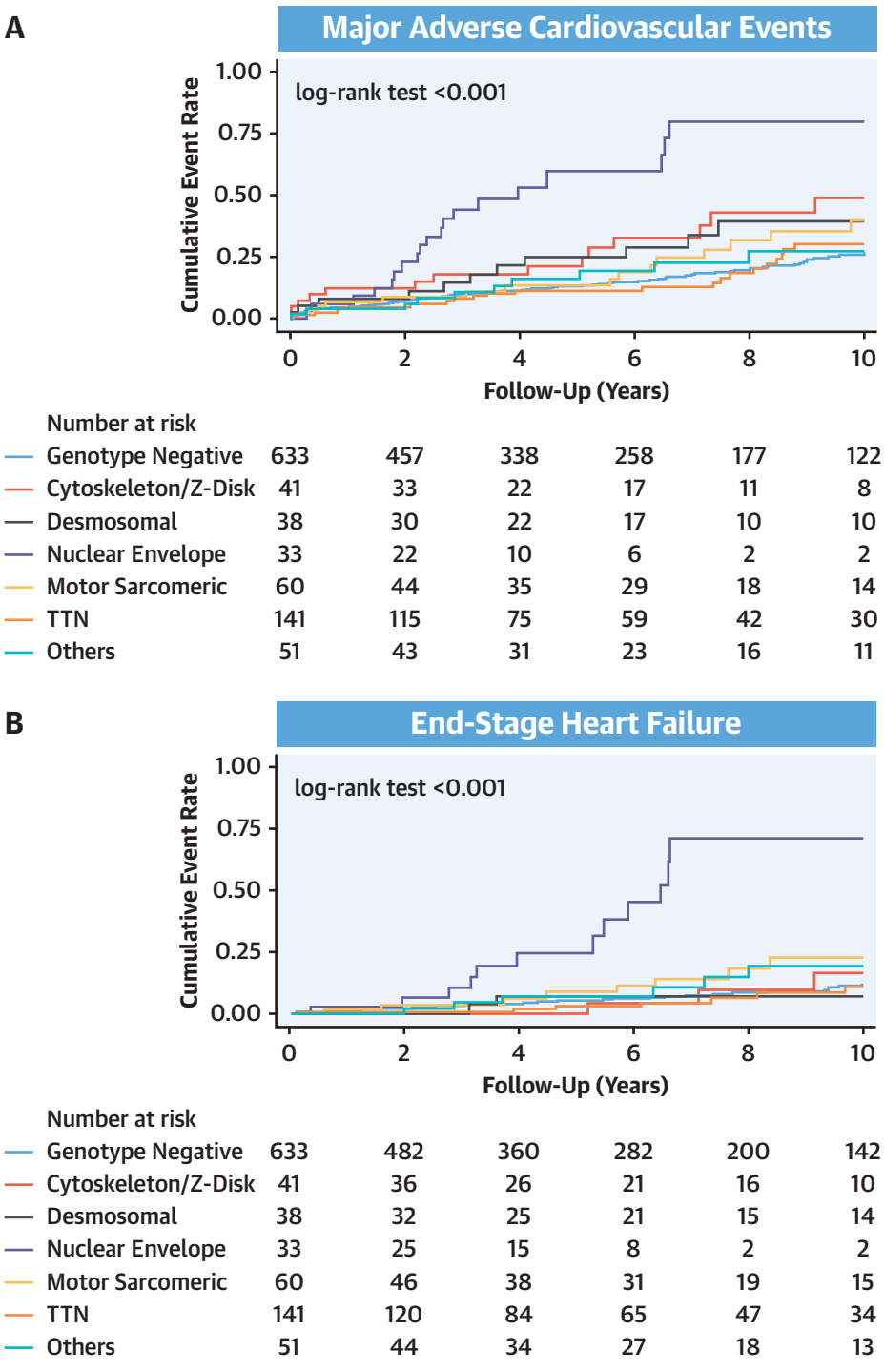
Our study adds to the available body of data to consider formulating the indications for ICD implantation in patients with nonischemic DCM. Although current clinical practice guidelines recommend LVEF for risk stratification of SCD and for guiding ICD implantation in DCM, this recommendation is still a matter of debate in nonischemic DCM (20,21). In the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality), prophylactic ICD implantation in patients with nonischemic DCM with LVEF ≤35% was not associated with improved survival (22). The results of the DANISH trial and subsequent meta-analyses suggest that using LVEF as the sole prognostic factor for predicting SCD is likely inadequate in DCM, and that additional factors are needed to identify individuals who would benefit from ICD implantation (23-25).

Our results indicate that carrying a DCM-causing variant is associated with MVA, particularly in patients with LVEF ≤35%. Accordingly, genetic testing can help guide prophylactic ICD implantation in DCM, and an ICD should be offered to genotype-positive DCM patients with LVEF ≤35%.

Interestingly, we found important differences between functional gene clusters in terms of arrhythmic risk, with a markedly higher rate of MVA in the nuclear envelope functional group in which genetic variants in *LMNA* predominated. These findings are consistent with previous reports showing higher arrhythmic risk in *LMNA*-related DCM (7,26). The cytoskeleton/Z-disk functional gene group also showed increased arrhythmic risk in our study. Variants in *FLNC* predominated in this group and *FLNC* mutations have also been associated with increased arrhythmic risk (27). Our data confirm these findings and support the recent recommendations of early ICD implantation in patients affected by certain genotypes (28).

Along the same line, we observed a trend toward a higher risk of MVA in genotype-positive patients with

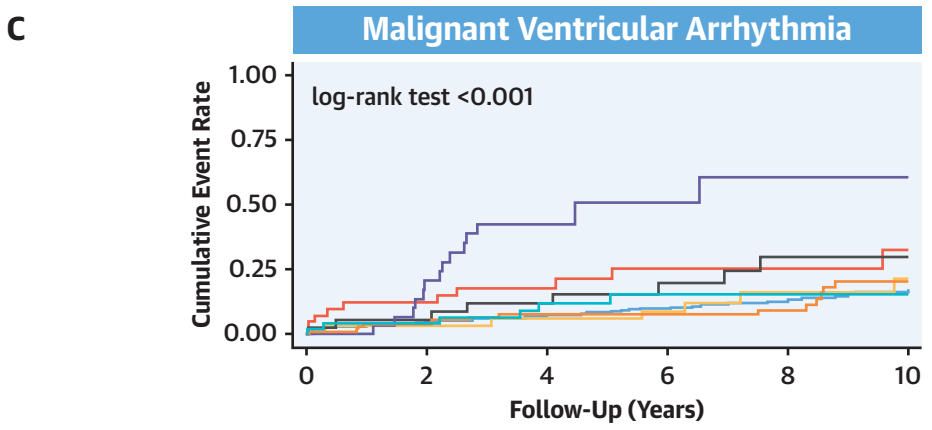
FIGURE 2 **Outcomes According to Functional Gene Group in Genotype-Positive Index Patients**



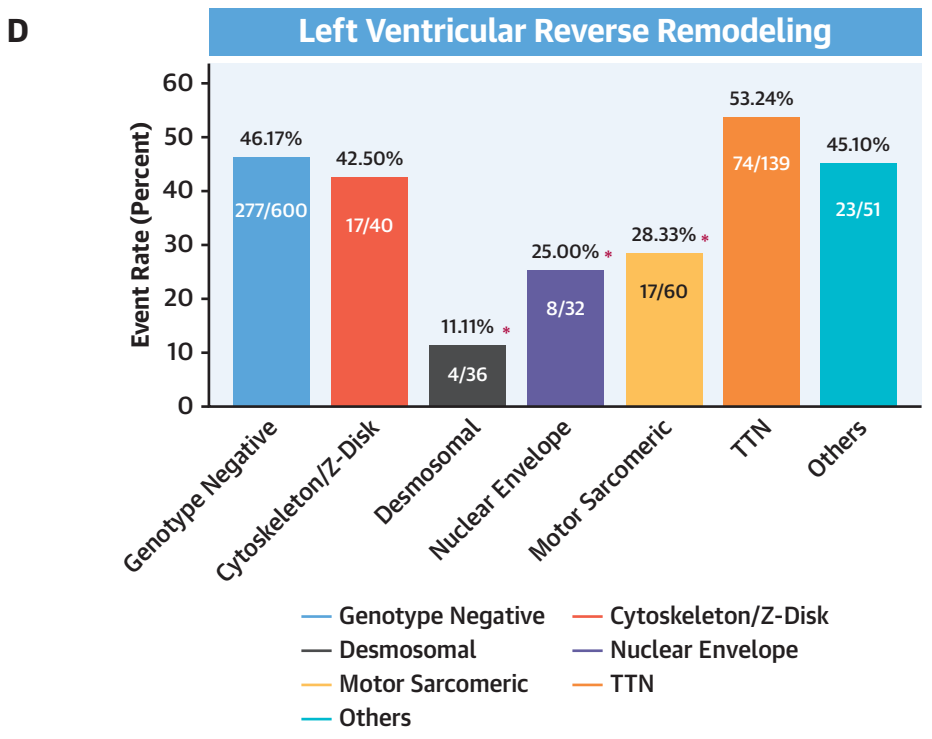
Cumulative incidence for composite **(A)** major adverse cardiovascular events, **(B)** end-stage heart failure, **(C)** malignant ventricular arrhythmia, and **(D)** left ventricular reverse remodeling rate at last follow-up according to functional gene group in genotype-positive dilated cardiomyopathy index patients. Patients with multiple pathogenic or likely pathogenic variants excluded. *$P < 0.001$ compared with the genotype-negative group.

Continued on the next page

FIGURE 2 Continued



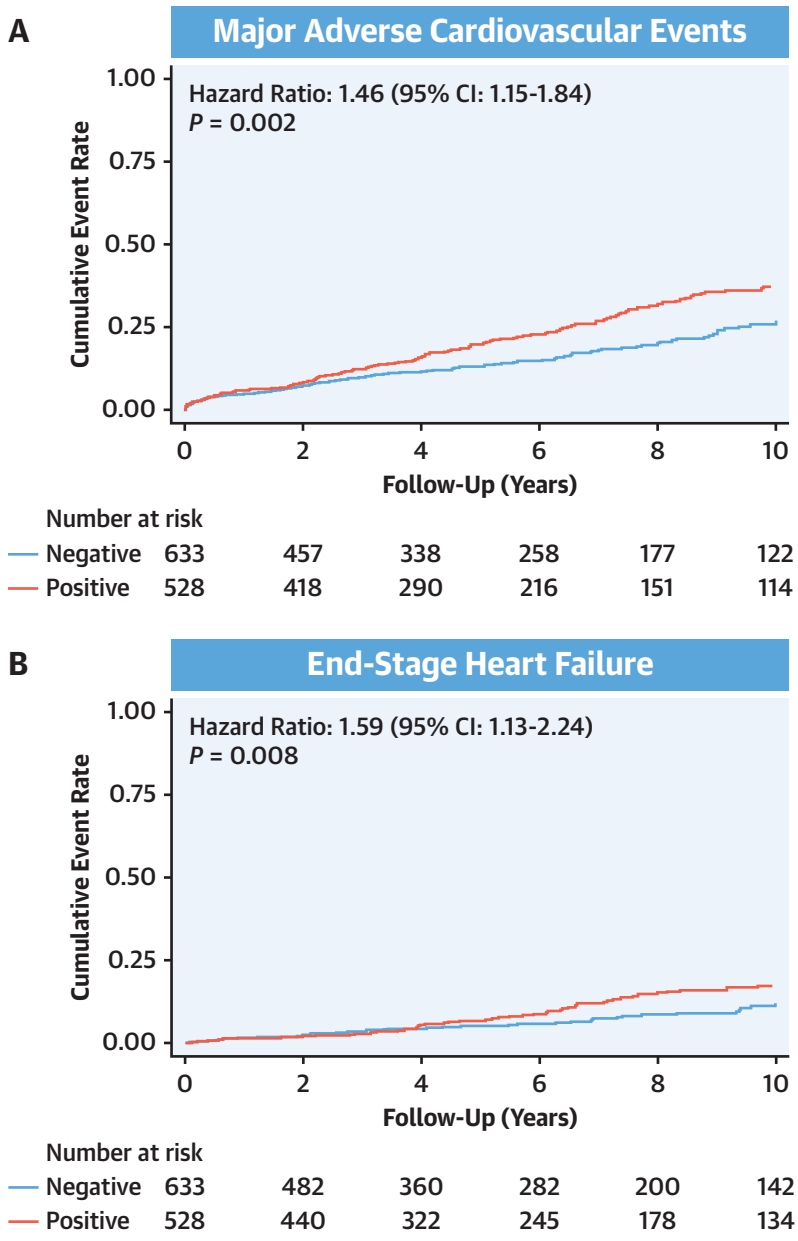
Number at risk						
Genotype Negative	633	464	346	265	181	125
Cytoskeleton/Z-Disk	41	33	22	18	13	9
Desmosomal	38	31	24	19	12	12
Nuclear Envelope	33	22	10	6	2	2
Motor Sarcomeric	60	45	35	29	18	15
TTN	141	116	77	60	44	29
Others	51	43	31	23	16	11



LVEF >35%, suggesting that some patients with specific genotypes could benefit from early ICD implantation, as in the case of *LMNA* mutations. However, larger genotype-phenotype correlation studies are needed to test this hypothesis and to identify who might benefit from this genetically tailored approach.

Genotype-positive patients also had worse evolution in terms of heart failure course, with a higher

FIGURE 3 **Outcomes in Genotype-Positive Versus Genotype-Negative Patients in the Overall Cohort**

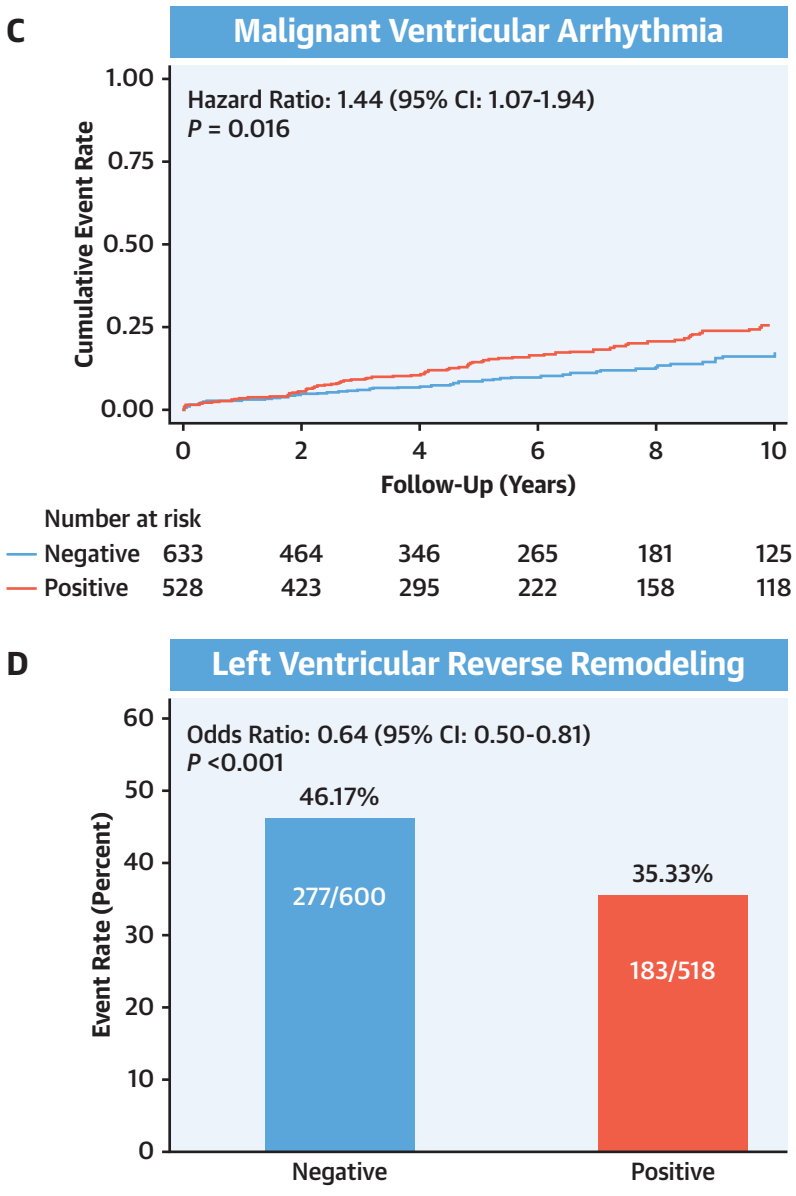


Cumulative incidence for composite **(A)** major adverse cardiovascular events, **(B)** end-stage heart failure, **(C)** malignant ventricular arrhythmia, and **(D)** left ventricular reverse remodeling rate at last follow-up in genotype-positive versus genotype-negative dilated cardiomyopathy patients from the overall cohort (N = 1,161). CI = confidence interval.

Continued on the next page

incidence of ESHF during follow-up and a worse response to medical treatment, as assessed by LVRR. Again, progression to ESHF and LVRR was not uniform across functional gene groups, opening the door to the adoption of an individualized prediction approach in DCM based on genetic features. In our study, a lower rate of LVRR was observed in desmosomal, nuclear envelope, and sarcomeric gene groups

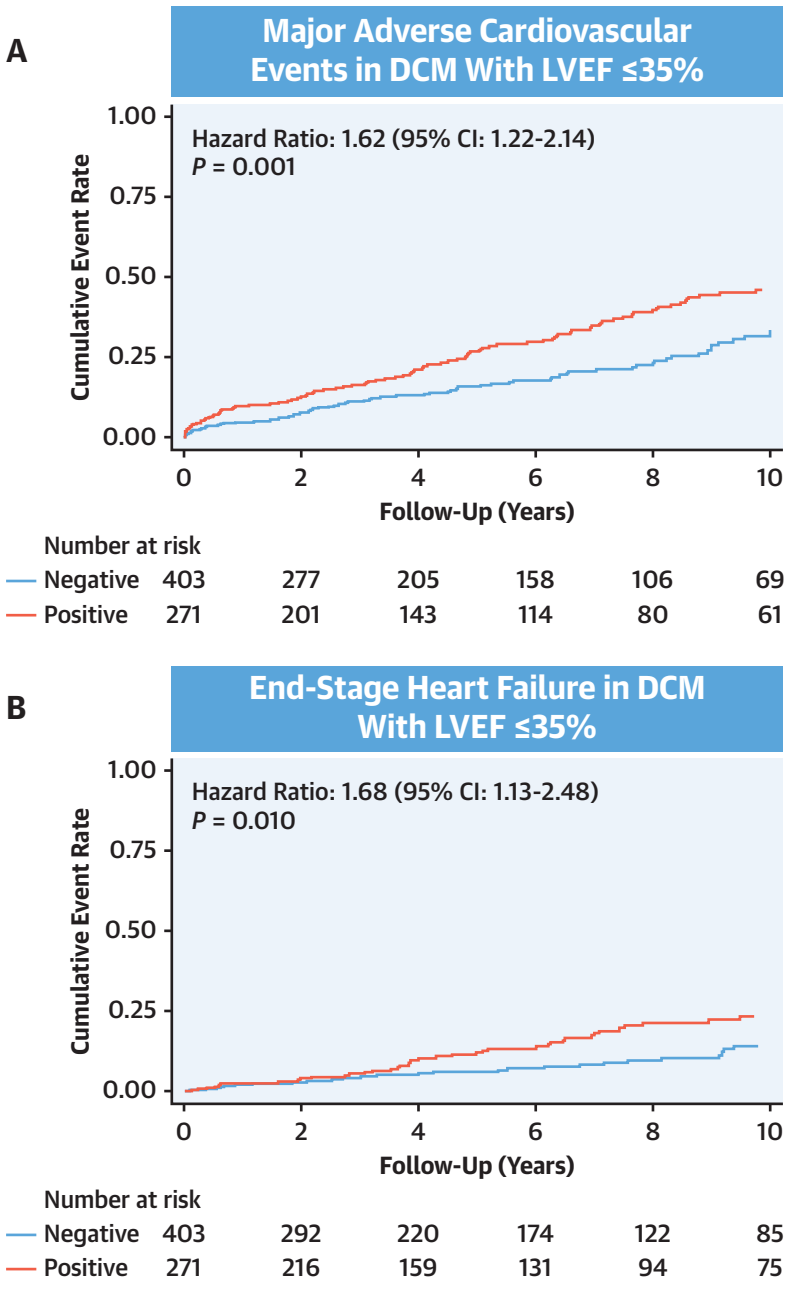
FIGURE 3 Continued



as compared with the better prognosis in the genotype-negative and the remaining gene groups. Interestingly, we did not find impaired reverse remodeling in patients with cytoskeleton/Z-disk variants, which contrasts with the findings of Dal Ferro et al (29). The higher number of patients with cytoskeleton/Z-disk variants, and stricter criteria applied to define disease-causing variants in our study, likely explains the difference. Additionally, our study confirms previous reports that suggested a more benign clinical course of DCM caused by *TTN*-truncating variants, with a lower incidence of ventricular arrhythmias when compared with other genes such as *LMNA* (16,30). In our study, the *TTN* group showed the lowest incidence of MACE and MVA and the highest rate of LVRR.

Overall, our results confirm that nonischemic DCM exhibits a marked phenotypic heterogeneity matched by its genetic heterogeneity, with an inverse relation across genetic groups between risk of adverse events and response to medical therapy assessed by LVRR. This precision medicine approach is particularly relevant when evaluating patients with nonischemic

FIGURE 4 Outcomes According to Genotype and LVEF in the Overall Cohort



Cumulative incidence for composite **(A)** major adverse cardiovascular events, **(B)** end-stage heart failure, **(C)** malignant ventricular arrhythmia in genotype-positive versus genotype-negative dilated cardiomyopathy (DCM) patients with left ventricular ejection fraction (LVEF) ≤35% and for composite **(D)** major adverse cardiovascular events, **(E)** end-stage heart failure, **(F)** malignant ventricular arrhythmia genotype-positive versus genotype-negative DCM patients with LVEF >35% at baseline from the overall cohort (N = 1,161). CI = confidence interval.

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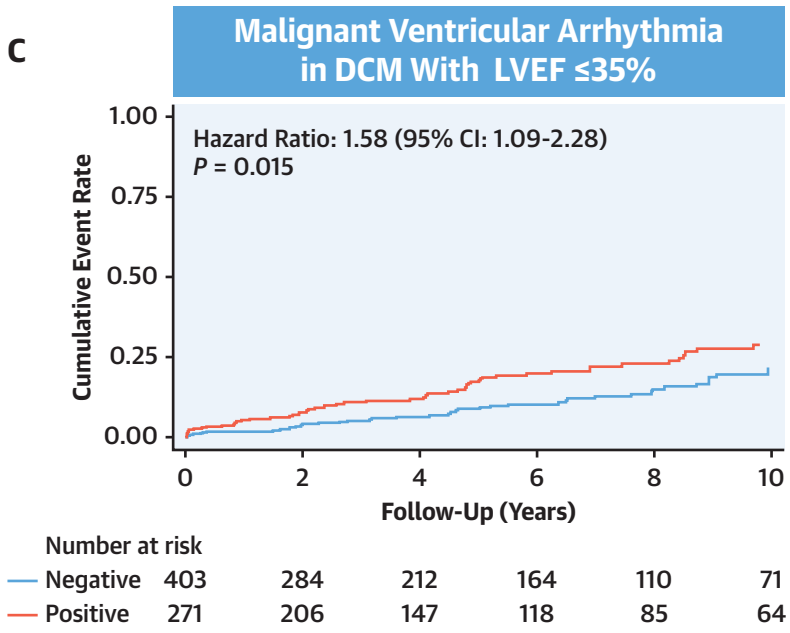
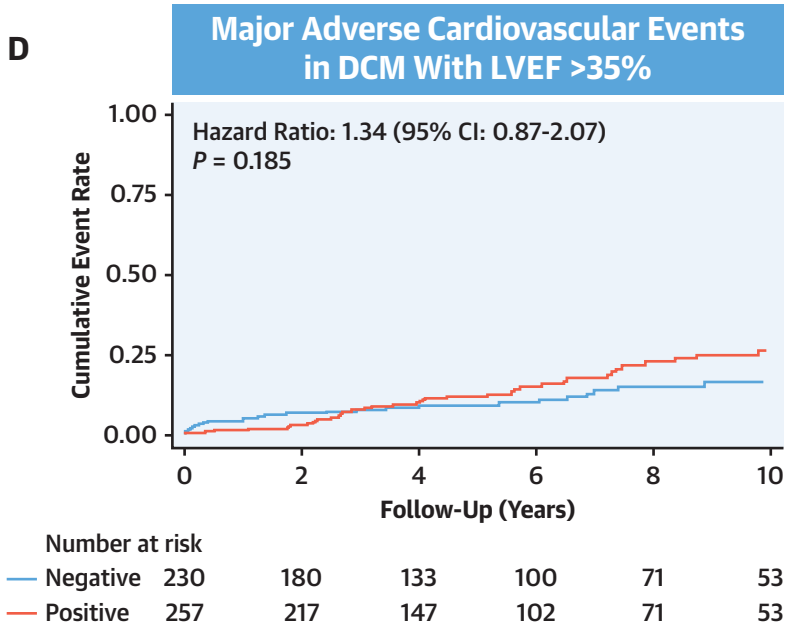
DCM and systolic dysfunction for whom decisions about referring for heart transplant evaluation or ICD implantation depend on the probability of achieving LVRR or experiencing MVA.

Thus far, DCM treatment has been dominated by a one-fits-all scheme with no or little therapeutic differences based on underlying etiology and genetic characteristics, which contrasts with what occurs in

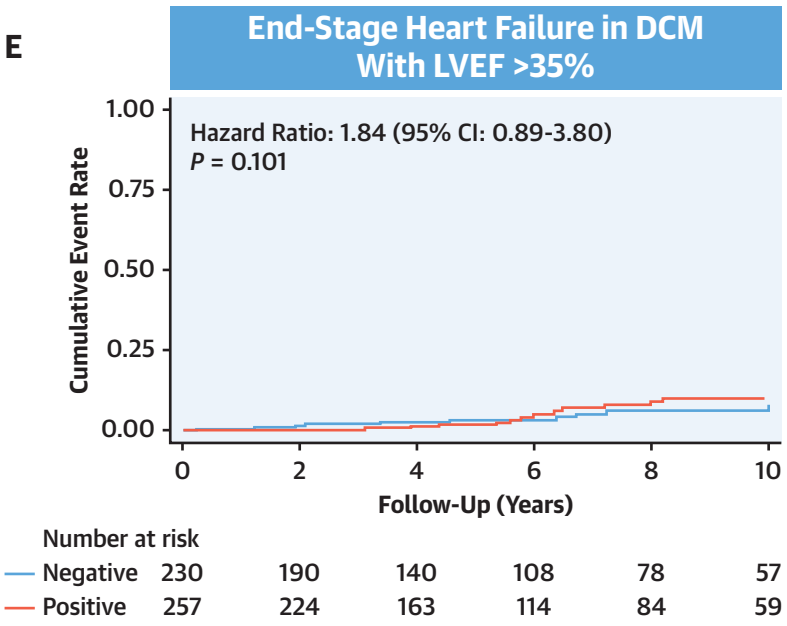
FIGURE 4 Continued

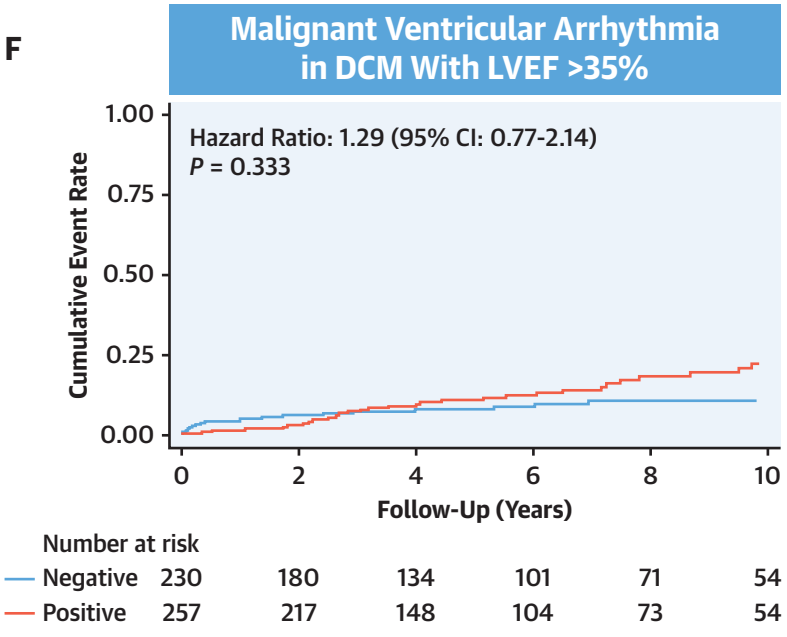




other areas of medicine such as oncology and hematology when treating certain malignancies. Although genetic testing in DCM is currently not recommended in the guidelines (20,21), we believe that genetic testing and, consequently, a precision medicine approach should become the standard of care also in cardiology when more data about the impact of genetic features on prognosis become available, and particularly if ongoing clinical trials with drugs directed specifically to certain genetic DCM subtypes show positive results (NCT03439514 and NCT04572893).

FIGURE 4 Continued

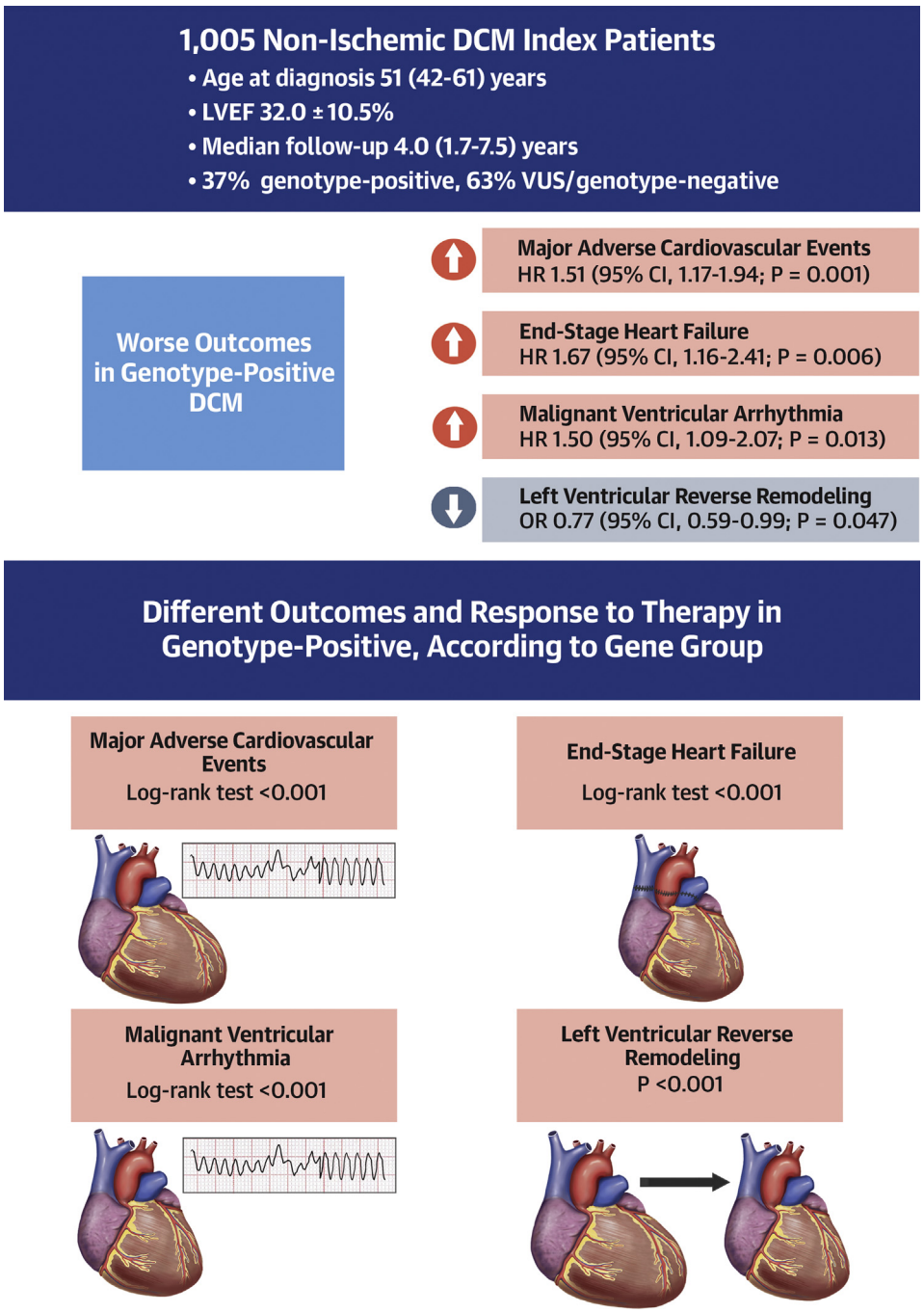




Future studies will need to address how to incorporate genetic data as a point-of-care tool for physicians and how to integrate this information with additional parameters such as those obtained from advanced imaging techniques, for example, cardiac magnetic resonance.

STUDY LIMITATIONS. Limitations of the study include its observational nature and retrospective design. Main DCM genes were evaluated in all cases, but the genes included in NGS target panels varied between centers and during time, reflecting the changes in the knowledge of DCM genetics in the last 5 years. Although this is the largest cohort of genotyped DCM patients with complete clinical outcomes published so far, the limited number of patients belonging to some functional gene groups restricts the power of the conclusions about these groups. Furthermore, participating centers were specialized

CENTRAL ILLUSTRATION **Clinical Outcomes in 1,005 Nonischemic Dilated Cardiomyopathy Patients According to Genotype**



Escobar-Lopez, L. et al. J Am Coll Cardiol. 2021;78(17):1682-1699.

Clinical outcomes of 1,005 genotyped dilated cardiomyopathy (DCM) index patients were retrospectively collected at 20 centers. Genotype-positive patients exhibited increased major adverse cardiovascular events, end-stage heart failure, and major ventricular arrhythmias and decreased left ventricle reverse remodeling compared with their genotype-positive peers. Clinical outcomes and left ventricle reverse remodeling varied depending on the underlying affected gene. CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; OR = odds ratio; VUS = variant of unknown significance.

inherited cardiac diseases and heart failure units and, therefore, findings might not be extrapolated to other settings.

CONCLUSIONS

Patients with DCM and with pathogenic or likely pathogenic variants had worse prognosis than genotype-negative patients, and clinical course and left ventricular remodeling varied depending on the underlying affected gene.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with nonischemic DCM and pathogenic or likely pathogenic genetic variants have worse prognosis than genotype-negative peers. Genetic testing is useful for risk stratification, and the results can predict prognosis and response to medical therapy.

TRANSLATIONAL OUTLOOK: Because penetrance of DCM-causing mutations is incomplete, further studies are needed to identify other factors governing development of DCM.

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KEY WORDS dilated cardiomyopathy, genetics, heart failure, left ventricular reverse remodeling, mutation, prognosis, sudden cardiac death, ventricular arrhythmia

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