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ORIGINAL ARTICLE

Sex Differences in Prognosis of Patients With Genetic Dilated Cardiomyopathy

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BACKGROUND: Dilated cardiomyopathy (DCM) is a genetically heterogeneous disease, presenting diverse clinical phenotypes and outcomes based on the underlying gene affected. The influence of sex on the gene-specific long-term prognosis of patients with genetic DCM remains unclear. This study aims to determine the effect of sex on the long-term prognosis per underlying genogroup.

METHODS: A retrospective cohort study was conducted using data from 4 international referral centers. Baseline and longitudinal clinical data of patients with DCM, with a median follow-up of 6.7 years (interquartile range, 3.5–11.9 years), were collected. The study included men and women with DCM who had undergone genetic testing. Patients were categorized into 7 genotype groups: cytoskeletal/Z-disk, desmosomal, nuclear envelope, motor sarcomeric, *TTN*, other genetic, and genotype negative. The main outcomes measured were left ventricular reverse remodeling, mortality, heart failure hospitalization, heart transplantation, and malignant ventricular arrhythmias.

RESULTS: Among 1716 patients, 1130 (66%) were men and 510 (30%) had a (likely) pathogenic variant. Ventricular remodeling was gene-dependent in women, with TTN patients exhibiting the highest rate (P=0.003) and desmosomal patients the lowest (P=0.04) compared with the genotype-negative group. After a median follow-up of 6.7 years, 334 men (29%) and 140 women (24%) reached the primary end point. Men with a (likely) pathogenic variant had the poorest prognosis, showing a higher rate of major adverse events (adjusted hazard ratio, 1.48 [95% CI, 1.12–1.95]; P=0.02) and malignant ventricular arrhythmias (adjusted hazard ratio, 1.83 [95% CI, 1.16–2.88]; P=0.009) compared with genotype-negative women. Prognosis varied by gene in men (log-rank P<0.0001) but not in women (log-rank P=0.1). The cytoskeletal/Z-disk, desmosomal, and nuclear envelope groups had the worst prognosis in men.

CONCLUSIONS: The genetic architecture and sex are critical predictors of left ventricular reverse remodeling and long-term prognosis in DCM. These factors should be integrated into individualized risk prediction models to enhance clinical outcomes in patients with DCM.

Key Words: genotype ■ heart failure ■ humans ■ phenotype ■ prognosis

Dilated cardiomyopathy (DCM) is a major cause of heart failure, with a prevalence of up to 1:250.[1] DCM is characterized by the presence of left ventricular dilation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease.[2] DCM has a genetic cause in around 40% of cases, with

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WHAT IS NEW?

- This is a large-scale, multicenter study to assess how both sex and genotype influence long-term outcomes in patients with dilated cardiomyopathy.
- It shows that males with pathogenic variants, especially in *LMNA*, *DSP*, and *FLNC*, have the poorest prognosis, with higher rates of adverse events and arrhythmias.
- Females exhibit genotype-specific differences in left ventricular reverse remodeling, particularly improved remodeling with *TTNtv* and poorer remodeling with *DSP* variants.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Genetic testing in dilated cardiomyopathy should be considered early in clinical practice irrespective of sex to identify high-risk patients, particularly those with *LMNA*, *DSP*, or *FLNC* variants.
- Genotype and sex should guide decisions on device therapy and risk stratification, especially for malignant arrhythmias.
- The gene-dependent nature of cardiac remodeling in females underscores the value of personalized follow-up strategies based on genetic background.
- These findings support the need for inclusive, sex-aware prediction tools, aiming to advance personalized and equitable care in genetic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
HFH	heart failure hospitalization
HR	hazard ratio
HTx	heart transplantation
IQR	interquartile range
LP	likely pathogenic
LVEF	left ventricular ejection fraction
LVRR	left ventricular reverse remodeling
MVA	malignant ventricular arrhythmias
NYHA	New York Heart Association

pathogenic or likely pathogenic (LP) variants found in a heterogeneous group of genes encoding for proteins of the sarcomere, cytoskeleton, mitochondria, sarcoplasmic reticulum, and proteins involved in calcium handling.[3] The genetic heterogeneity in DCM is also reflected in the clinical phenotype and outcomes, which differ depending on the underlying affected gene.[4–6] These phenotypic differences are translated into gene-specific risk prediction models for clinical practice.[7–9] For example, the risk prediction model of *LMNA* contains nonmissense variants, left ventricular ejection fraction (LVEF), nonsustained ventricular tachycardia, atrioventricular block, and male sex as gene-specific risk factors.[8]

Despite the historical underrepresentation of women in clinical trials,[10] recent efforts highlight the significance of DCM in women, with sex emerging as an important factor influencing DCM outcomes. In general, men have a worse prognosis compared with women with regards to transplant-free and overall survival in DCM, which might be to the consequence of more severe left ventricular remodeling and dysfunction.[11] Moreover, there is a notable gap in long-term data (ie, beyond 5 years) on sex differences in DCM outcomes.[12]

The influence of sex on left ventricular remodeling and prognosis in genetic DCM remains largely unknown. Accordingly, this study explored the influence of sex on the gene-specific, long-term prognosis of genotyped DCM patients in a multicenter cohort.

METHODS

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

Study Population

The study comprises a multicenter, observational, and longitudinal study of genetically tested patients with DCM recruited from inherited cardiac diseases and heart failure units at 4 international hospitals; Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands; Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain; United Hospitals of Trieste University Hospital, Trieste, Italy; University of Colorado Anschutz Medical Campus, Aurora. The cohort from the Netherlands was derived from the Maastricht Cardiomyopathy Registry, which prospectively includes individuals with heart failure-like symptoms or who underwent cardiac and genetic testing from 2004 onwards.[13] The cohort from Italy was derived from the Heart Muscle Disease Registry of Trieste Registry that started including patients prospectively in 1979. The cohort from Spain was from the Hospital Puerta de Hierro's Inherited Cardiac Diseases Unit in Madrid, and the cohort from the United States was derived from the Familial Cardiomyopathy Registry. The current study selected all patients with DCM who underwent genetic testing. All included patients were probands.

The DCM diagnosis was defined according to the World Health Organization criteria and the latest European Society of Cardiology proposal.[14,15] Enrolled patients presented with an LVEF <50%, without the presence of occlusion of a major coronary artery branch at coronary angiography, pericardial diseases, congenital heart diseases, cor pulmonale, and active myocarditis. Patients, when not contraindicated, received guideline-directed medical therapy titrated to the maximal tolerated dose as well as device therapy according to the latest European Society of Cardiology and AHA/ACC guidelines.[15,16] Only patients aged >16 years at the time of diagnosis were included. Data at participating centers were extracted from clinical records using a uniform methodology. The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethics Committee of all participating institutions. All individuals provided written informed consent.

Clinical Evaluation of Patients With DCM

Baseline evaluation was defined as the first outpatient clinic visit of a patient with DCM in the medical center that enrolled the patient. As part of the diagnostic protocols in participating centers, the selected patients all underwent genetic testing after genetic counseling, a physical examination, blood sampling, a 12-lead ECG, echocardiogram, and systematic follow-up. Baseline data regarding demographics; age of diagnosis, New York Heart Association (NYHA) class, family history of DCM and sudden cardiac death, and peripartum presentation were collected, as well as classic cardiovascular risk factors; hypertension, hypercholesterolemia, diabetes, and BMI. Furthermore, data regarding Implantable Cardioverter Defibrillator and CRTD implantations at baseline and during follow-up were collected. Although individual-level ancestry data were not collected due to legal constraints, the vast majority of the cohort is composed of individuals of European non-Finnish ancestry. Furthermore, data regarding guideline-directed medical therapy started at diagnosis for β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonist, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, loop diuretics, and SGLT-2 inhibitors were collected. In addition, the percentage of optimal medical therapy for β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonisst, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and SGLT-2 inhibitors was also reported. Optimal medical therapy was defined as reaching 100% of the recommended dosage for heart failure medication.

Genetic Testing and Variant Classification

Participating individuals received genetic testing using targeted next-generation sequencing panels. All patients underwent genetic testing from 2014 onwards. The specific gene panels used by each center per time period are depicted in the Supplemental Methods: Genetic testing approach per center. All patients were tested for the 18 genes most robustly associated with DCM (these include *ACTC1, BAG3, DMD, DES, DSP, EMD, FLNC, LMNA, MYH7, NEXN, PLN, RBM20, SCN5A, TNNC1, TNNI3, TNNT2, TTN, TPM1,* and *VCL*), with the exception of *FLNC* in Maastricht, which was included in the testing protocol starting in 2018.

All variants were classified according to the ACMG guidelines.[17] In addition, all variants were reevaluated by genetic molecular specialists in Maastricht to ensure consistency and a uniform variant interpretation. Only patients with a LP or pathogenic variant (pathogenic/LP; class 4 or 5) were scored in the group who received a genetic diagnosis (genotype positive). To create a coherent genotype-based classification for analyses, patients sharing pathogenic/LP variants in genes belonging to the same subcellular compartment were clustered together: (1) cytoskeleton/Z-disk, (2) desmosomal, (3) TTN, (4) nuclear envelope, (5) motor sarcomeric, (6) other genetic, or (7) genotype negative, as described before.[18]

Transthoracic Echocardiography

Echocardiographic measurements were performed in the standard parasternal, apical, and subxiphoidal views at baseline and after 1-year follow-up. Follow-up echocardiography after 1 year (±200 days) was available in 1323 (77%) patients. Left ventricular reverse remodeling (LVRR) was defined as an absolute increase of ≥10 points or LVEF ≥50% with at least a 5-point improvement.[19] Echocardiography observers were blinded to clinical and genetic parameters.

Outcomes

Patients were followed for a median of 6.7 years (interquartile range [IQR], 3.5–11.9 years). Follow-up data on mortality, heart transplantation (HTx), malignant ventricular arrhythmia events (MVA), and heart failure hospitalization (HFH) were collected using patients' medical records, municipal population registers, and telephone contact with general practitioners. Patients with no events were censored at the date of the last available follow-up. MVA were defined as nonfatal ventricular fibrillation (with or without Implantable Cardioverter Defibrillator shock), hemodynamic unstable sustained ventricular tachycardia, and sustained ventricular tachycardia with appropriate Implantable Cardioverter Defibrillator shock. Mortality was categorized into heart failure-related death (HFD), sudden cardiac death, and other causes of death. Sudden cardiac death was defined as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive. The primary end point was the combination of mortality, HFH, HTx, and MVA and as a secondary end point, we focused solely on MVA. In addition, major heart failure events were the combination of mortality, HFH, and HTx.

Statistical Analysis

Groups were compared using Student *t* test or the Mann-Whitney *U* test, or ANOVA or the Kruskal-Wallis test when comparing >2 groups. Noncontinuous categorical variables are expressed as counts (percentages) and were compared using the χ^2 or Fisher exact test, as appropriate. We applied the Bonferroni correction to adjust for multiple testing. The Kaplan-Meier survival curves were estimated and differences were assessed by the log-rank test. The 95% CIs for survival probabilities at specified time points were estimated around the Kaplan-Meier survival proportions. Cox proportional hazards regression analysis was performed to assess the association of sex and genetic status with event-free survival. To confirm the Cox model's assumption of proportional hazards, tests based on Schoenfeld residuals revealed no significant deviations. Multivariate mixed-effect Cox modeling was used to adjust the fixed effect of age and LVEF, and the fixed effect of different centers with a frailty term. We conducted Cox proportional hazards regression analysis to evaluate the interaction effects between sex and genotype on time-to-event outcomes, incorporating interaction terms directly into the model to assess their significance and impact on hazard ratios. The significance of the effect of interaction between sex and genotype was tested by an analysis of deviance table for mixed-effect Cox models (ANOVA). To account for competing risks from noncardiac death in the analysis of MVA, a sensitivity analysis using Fine and Gray hazard models was performed. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY) and R Studio, and visualized using GraphPad Prism, version 10.2.0. The survival analysis of the data was done using the survival package (v3.5-5). Statistical significance was defined

as the null hypothesis (hazard ratio [HR]=1) did not fall within the 95% CI, equivalent to $P<0.05$.

RESULTS

Clinical Parameters

The study population consisted of 1716 patients with DCM of which 1130 were men (66%) (Table; Table S1). A total of 510 patients had a (likely) pathogenic variant (30%), of which 344 were men (67%). Patients were divided into 7 genogroups depending on the underlying affected gene (cytoskeleton/Z-disk (n=60), desmosomal (n=32), nuclear envelope (n=65), motor sarcomeric (n=89), *TTN* (n=222), other genetic (n=42), or genotype negative (n=1206); Tables S2 through S4).

In the genotype-positive group, the median age of diagnosis was 48 years (IQR, 37–57 years) in men and 49 years (IQR, 36–60 years) in women with DCM (*P* value 0.40, Table). In the genotype-negative group, the median age of diagnosis in men was 54 years (IQR, 44–62 years) and in 54 years (ICR, 43–62 years) in women

Table. Characteristics of Patients With DCM Stratified by Sex and genetic Status (n=1716)

	Genotype positive (n=510)			Genotype negative (n=1206)		
	Men (n=344)	Women (n=166)	*P* value	Men (n=785)	Women (n=420)	*P* value
Genotype						
Genotype positive, (%)	**344 (30)**	**166 (28)**	**0.34**	…	…	…
Cytoskeletal/Z-disk, n (%)	36 (10)	24 (14)		…	…	…
Desmosomal, n (%)	10 (3)	22 (13)		…	…	…
Nuclear envelope, n (%)	46 (13)	19 (11)		…	…	…
Motor sarcomeric, n (%)	60 (17)	29 (17)		…	…	…
TTN, n (%)	165 (48)	57 (34)		…	…	…
Other genetic, n (%)	27 (8)	15 (9)		…	…	…
Demographics at baseline						
Age of diagnosis, ICR	48 (37–57)	49 (36–60)	0.40	54 (44–62)	54 (43–62)	0.90
Family history of DCM (%)	181 (54)	95 (60)	0.29	130 (17)	99 (24)	0.004
Family history of SCD (%)	64 (19)	36 (23)	0.40	106 (14)	80 (20)	0.01
Hypertension (%)	67 (20)	28 (18)	0.54	228 (30)	119 (29)	0.89
Hypercholesterolemia (%)	59 (18)	15 (10)	0.02	133 (18)	74 (18)	0.74
Diabetes (%)	46 (14)	5 (3)	<0.0001	114 (15)	36 (9)	0.99
BMI >30 (%)	53 (17)	29 (19)	0.51	191 (27)	91 (24)	0.002
Peripartum presentation (%)	…	6 (4)	…	…	22 (5)	…
Device implantation during follow-up						
ICD implantation (%)	151 (46)	68 (43)	0.63	226 (28)	94 (23)	0.02
CRTD implantation (%)	32 (10)	8 (5)	0.11	146 (19)	59 (15)	0.06
NYHA class at baseline						
NYHA class ≥3 (%)	55 (17)	33 (21)	0.38	117 (17)	73 (20)	0.27
I (%)	152 (48)	64 (40)		312 (46)	117 (32)	
II (%)	112 (35)	63 (39)		255 (37)	177 (48)	
III (%)	48 (15)	29 (18)		104 (15)	66 (18)	
VI (%)	7 (2)	4 (3)		13 (2)	7 (2)	
Baseline echocardiogram						
LVEF±SD	34±12	34±12	0.85	34±13	34±12	0.57
LVEF <35%, n (%)	174 (52)	93 (57)	0.30	401 (52)	203 (49)	0.39
1-year follow-up echocardiogram						
LVEF±SD	39±12	40±12	0.52	39±12	39±13	0.76
LVEF <35%	88 (33)	37 (31)	0.90	205 (34)	118 (37)	0.35
LVRR, n (%)	102 (39)	51 (43)	0.50	239 (39)	105 (33)	0.07

Baseline characteristics are shown per genetic status and stratified by sex. Values are presented as number (percentage), mean±SD, or median (interquartile range), as appropriate. BMI indicates body mass index; CRTD, cardiac resynchronization therapy with defibrillator; DCM, dilated cardiomyopathy; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; NYHA, New York Heart Association; and SCD, sudden cardiac death.

with DCM. All patient groups presented with a mean LVEF of 34% at baseline. No significant differences were observed between men and women in NYHA class ≥3 in both the genotype positive and genotype-negative group. Diabetes was more prevalent in genotype-positive men than in genotype-positive women ($P<0.0001$). A family history of DCM was more often observed in genotype-negative women than in genotype-negative men (P value 0.004). Prescribed medical therapies and optimal medical therapy at baseline based on genotype status and LVRR per sex can be found in Table S5.

LVRR in Men and Women With Genetic DCM

Follow-up echocardiography data was available in 1.323 (77%) patients. The LVEF at 1 year follow-up did not differ between men and women for both genotype positive and genotype-negative DCM patients (genotype positive: 39±12% men and 40±12% women, P value 0.52; and genotype negative 39±12% men and 39±13% women, P value 0.76; Table). The rate of LVRR did not differ between men and women (genotype positive: 39% versus 43%, P value 0.50; and genotype negative: 39% versus 33%, P value 0.07; Figure 1A; Table). However, LVRR differed depending on the underlying affected genogroup (overall P value 0.01; Figure 1B), showing a significantly worse LVRR rate in the desmosomal genogroup and a better LVRR rate in the TTNtv genogroup compared with genotype negative. This was observed in women but not in men (overall P value 0.003 and P value 0.60, respectively; Figure 1C and 1D). Women with DCM due to variants in desmosomal genes have a lower rate of LVRR (P value 0.04) while those with DCM due to TTNtv have a higher rate of LVRR compared with the genotype-negative women (P value 0.001).

Effect of Sex and Genotype on Long-Term Outcome

A total of 328 men (29%) and 139 women with DCM (24%) reached the primary end point after a median follow-up of 6.7 years (IQR, 3.5–11.9 years). There

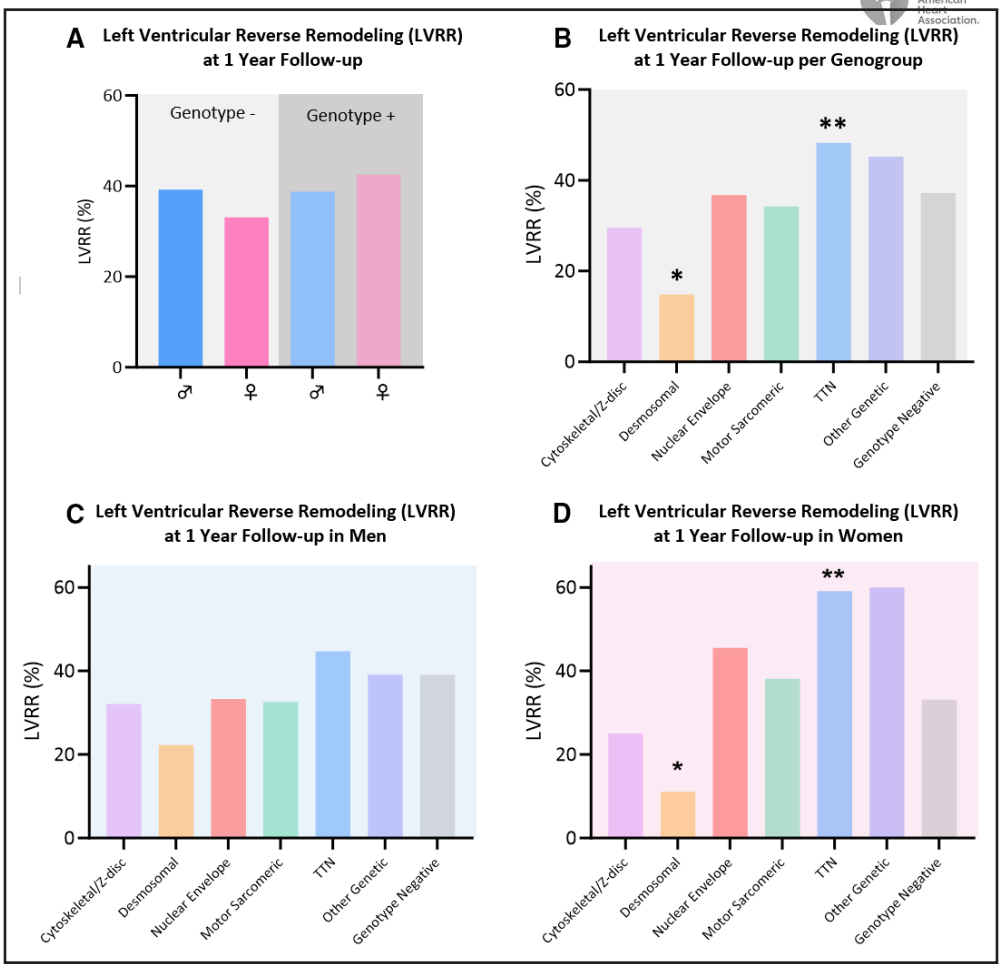

Figure 1. Percentage of left ventricular reverse remodeling (LVRR) at 1-year follow-up in men and women with dilated cardiomyopathy (DCM).
A, LVRR per genetic status and sex. **B**, LVRR per genogroup. **C**, LVRR per genogroup in men. **D**, LVRR per genogroup in women. Fisher exact test was used to compare the genotype-negative group to the individual genogoups. *$P<0.05$, **$P<0.01$.

were no significant differences in major adverse events (including mortality, HTx, MVA, and HFH) when comparing men and women (log-rank *P* value 0.07; Figure 2A), although women had a significantly lower event rate after adjustment for age, LVEF at baseline, NYHA class, and center (HR, 0.79 [95% CI, 0.64–0.96]; *P* value 0.02). There were no differences in major adverse events when stratified by sex and the presence of a pathogenic/LP variant (log-rank *P* value 0.20; Figure 2B). However, after adjusting for age, LVEF at baseline, NYHA class, and center, men with a genetic variant had a significantly increased rate of major adverse events compared with genotype-negative women (HR, 1.48 [95% CI, 1.12–1.95], *P* value 0.006, 5-year risk of 18%, Figures 3A and 4). We did not observe an interaction between sex and genotype on major adverse events (P_{int}=0.54; Figure 3A). No differences were observed between men and women in HFD and sudden cardiac death (Figure S1).

After stratification per genogroup, differences in the primary end point major adverse events were observed in men (log-rank *P*<0.0001, Figure 2C), but not in women with DCM (log-rank *P* value 0.09; Figure 2D). Men and women with DCM due to a pathogenic/LP variants in nuclear envelope genes had an increased rate of major adverse events after adjustment for age, LVEF at baseline, and center compared with patients with DCM without a genetic variant (HR, 2.52 [95% CI, 1.68–3.79], *P*<0.001 in men and HR, 4.20 [95% CI, 2.01–8.80], *P*<0.001 in women; Figure 3B). Survival analysis and forest plots for major adverse events per genogroup irrespective of sex can be found in Figure S2.

Effect of Sex and Genotype on Malignant Arrhythmogenic Events

A sex-specific difference was observed in the survival distribution of MVA, showing that men have an increased rate of MVA compared with women with DCM (log-rank *P* value 0.0002; Figure 2E). Further stratification based on genotype showed that men with DCM and a genetic variant had the highest rate of MVA compared with the other groups (log-rank *P*<0.0001; Figure 2F) and after adjusting for age, baseline LVEF, NYHA class, and center (HR, 1.83 [95% CI, 1.16–2.88], *P* value 0.009, 5-year risk of 11%; Figures 3C and 4). However, no statistical interaction between sex and genotype on malignant ventricular arrhythmias was detected (P_{int}=0.29; Figure 3A).

Genogroup-specific differences were observed for the occurrence of MVA (log-rank *P*<0.0001 for men and *P* value 0.10 for women; Figure 2G and 2H). Men with DCM and a pathogenic/LP variant in cytoskeletal/Z-disk, desmosomal, and nuclear envelope genes had an increased rate of MVA compared with the men with DCM without a genetic variant after adjustment for age, LVEF at baseline, and center (Figure 3D). The same trend was also observed among women with pathogenic/LP variants in the desmosomal genes, although not statistically significant. In addition, women with a TTNtv have a lower risk for MVA compared with genotype-negative women. However, this observation was not statistically significant. The overall difference in the rate of MVA between genogroups in men also remained after exclusion of patients with DCM due to a pathogenic/LP variant in nuclear envelope genes,

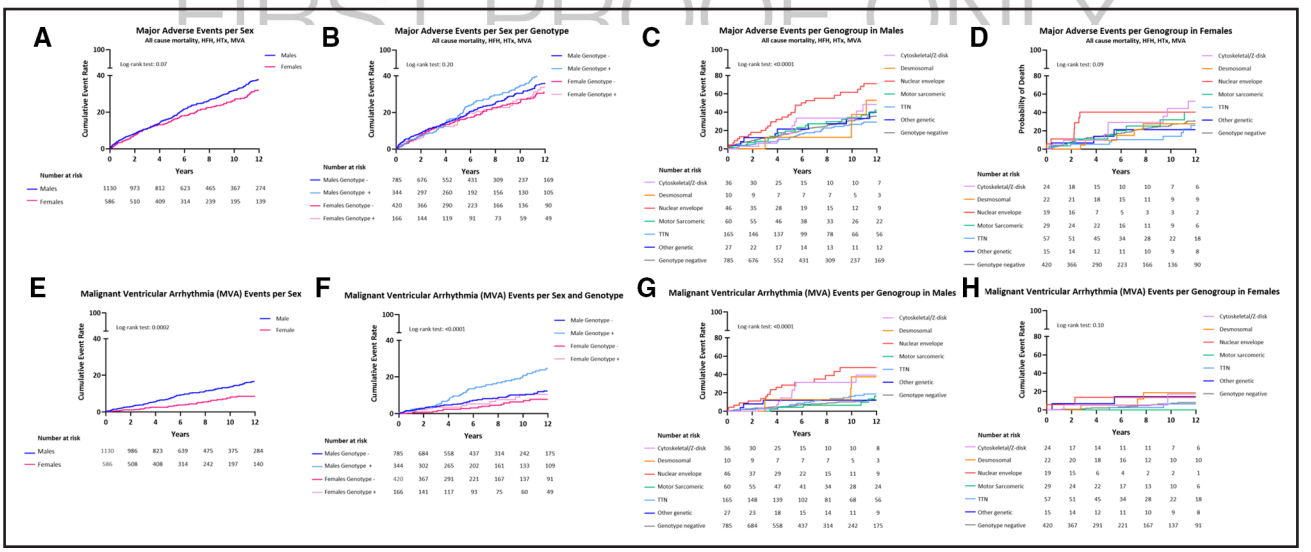

Figure 2. Cumulative incidence curves demonstrating the occurrence of the primary and secondary end point stratified by genogroups in men and women with dilated cardiomyopathy (DCM).
A, Major adverse events (all-cause mortality, heart failure hospitalization [HFH], heart transplantation [HTx], malignant ventricular arrhythmia [MVA]) stratified by sex. **B**, Malignant ventricular arrhythmia (MVA) events stratified by sex. **C**, Major adverse events stratified by sex and genetic status. **D**, MVA events stratified by sex and genetic status. **E**, Major adverse events stratified by genogroup in men with DCM. **F**, MVA events stratified by genogroup in men with DCM. **G**, Major adverse events stratified by genogroup in women with DCM. **H**, MVA events stratified by genogroup in women with DCM.

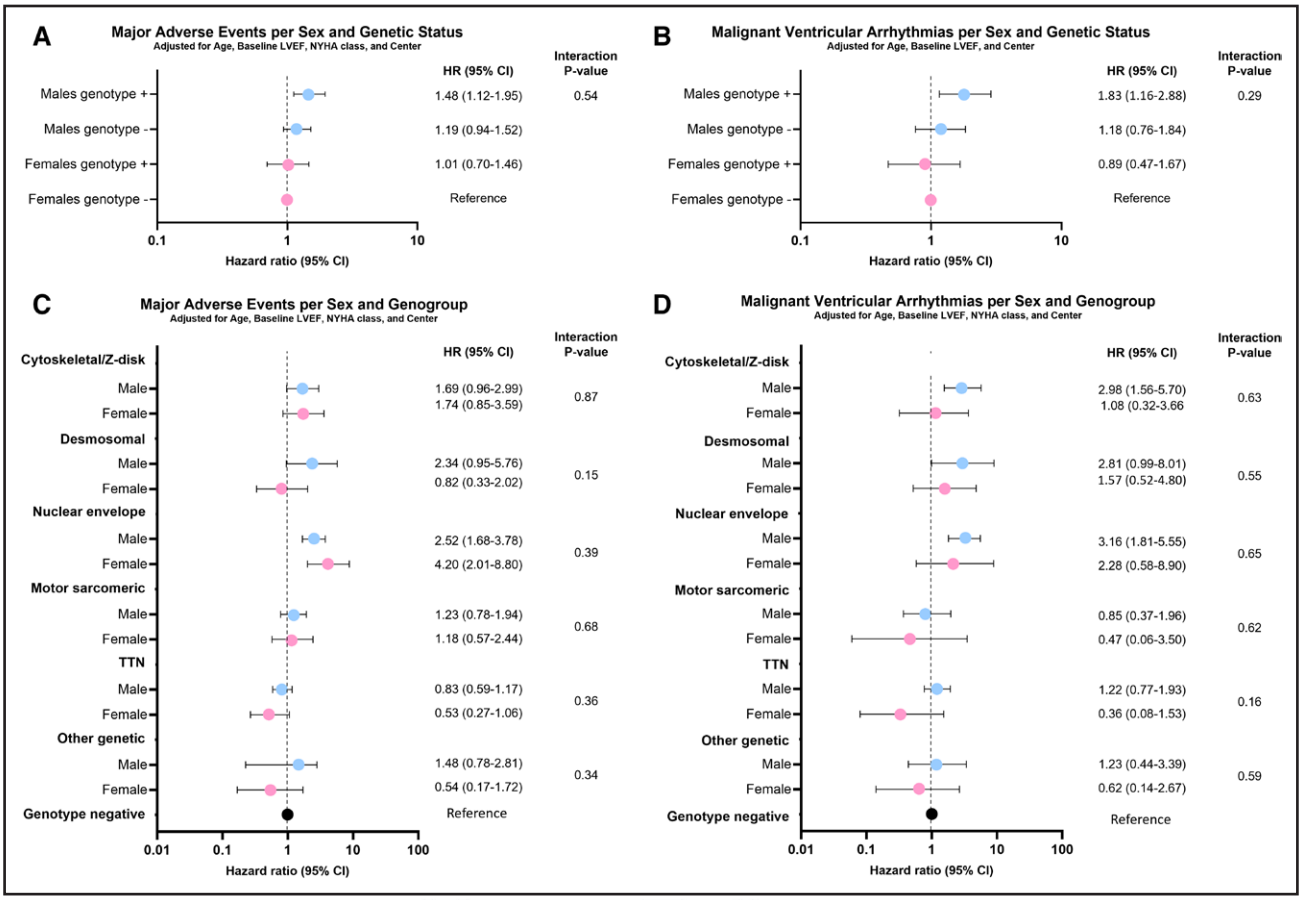

Figure 3. Forest plots demonstrating age, left ventricular ejection fraction (LVEF) at baseline, New York Heart Association (NYHA) class, and center (frailty model) adjusted hazard ratios (95% CI) for the primary and secondary end points stratified by sex and genotype.

Interaction between genogroup and sex was tested. **A**, Adjusted Cox proportional hazard ratios for major adverse events (all-cause mortality, heart failure hospitalization [HFH], heart transplantation [HTx], malignant ventricular arrhythmia [MVA]) per sex and genetic status. **B**, Adjusted Fine and Gray hazard ratios for MVA events per sex and genetic status. **C**, Adjusted Cox proportional hazard ratios for major adverse events stratified by genogroup and sex. **D**, Adjusted Fine and Gray hazard ratios for MVA events stratified by genogroup and sex.

enriched with *LMNA* that is known to be arrhythmogenic (log-rank *P* value 0.003; Figure S3A), which was not observed in women (log-rank *P* value 0.28; Figure S3B). Survival analysis and forest plots for MVA per genogroup irrespective of sex can be found in Figure S2.

There were no differences in major heart failure events (mortality, HFH, and HTx) stratified per sex (log-rank *P* value 0.60; Figure S4A), and per sex and genotype (Log-rank *P* value 0.74; Figure S4B). Furthermore, the occurrence of major heart failure events was dependent on the underlying genogroup in men with DCM, but not in women with DCM (log-rank $P<0.0001$ and 0.08, respectively; Figure S4C and S4D).

DISCUSSION

This study examined the sex-related impact on genotype-specific long-term outcomes in one of the largest multicenter cohort of patients with DCM. The worst prognosis was observed in men with a pathogenic/LP variant, showing a heightened rate of major adverse events (a composite of all-cause mortality, heart transplantation, hospitalization for heart failure, or malignant ventricular arrhythmias) and in particular malignant ventricular arrhythmias. In men, the rate of major adverse events and malignant ventricular arrhythmias was associated with the specific underlying genotype, while the impact of genotype on outcome in women with DCM was less definitive in our study. Both men and women with a pathogenic/LP variant in cytoskeletal/Z-disk, desmosomal, and nuclear envelope genes had an increased risk for malignant ventricular arrhythmias. In women, the rate of LVRR was dependent on their specific genotype, which was not observed in men.

Effects of Sex and Genotype on Outcome and Cardiac Function

A detailed description of differences in long-term outcome focusing on men and women in a large genotyped, international DCM cohort was lacking. Genotype-positive men have the highest rate of adverse events, primarily

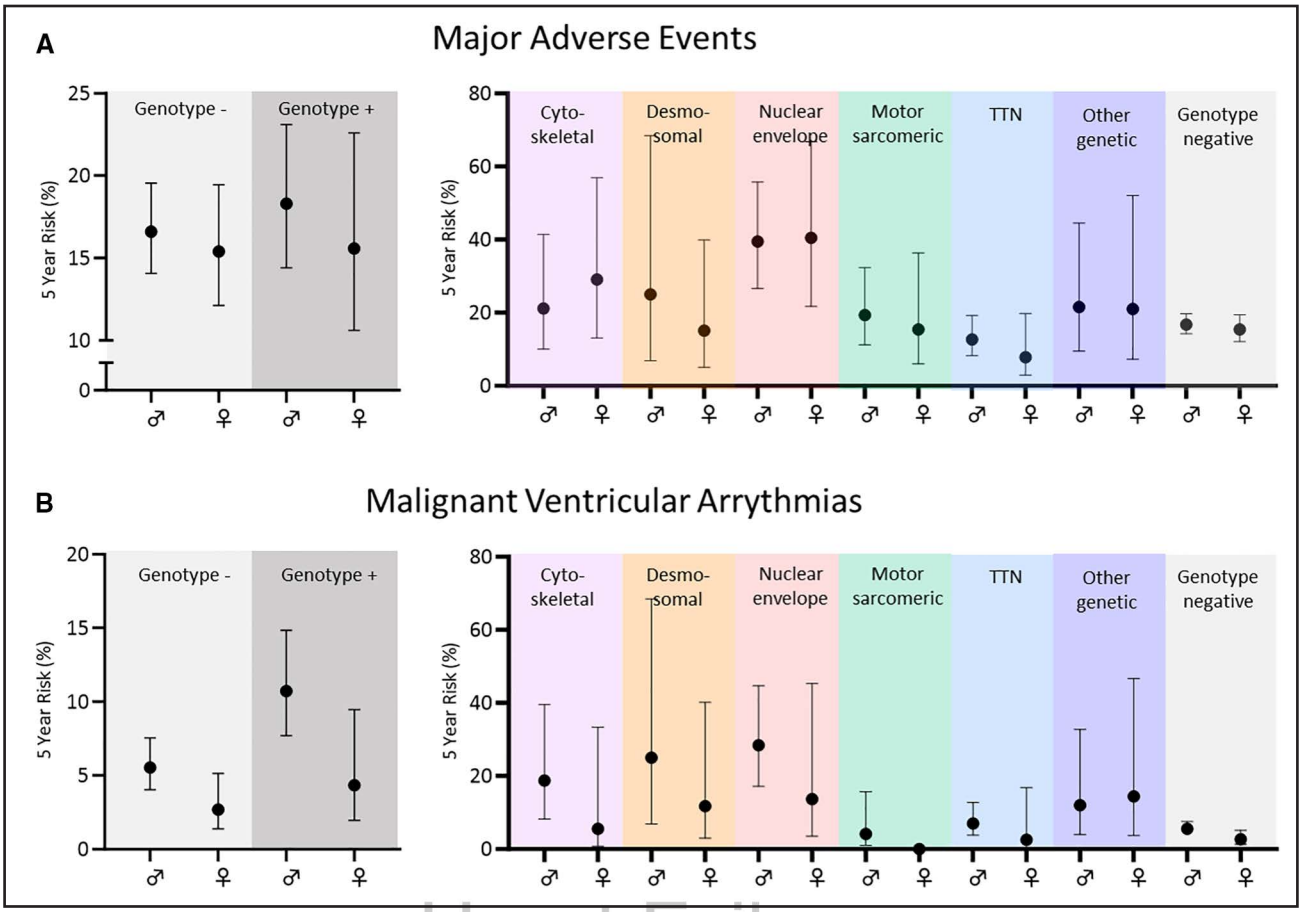

Figure 4. Five-year cumulative incidence estimates (with 95% CIs) for the primary and secondary end points in men and women with dilated cardiomyopathy (DCM).

A, Unadjusted 5-year risk of major adverse events (all-cause mortality, heart failure hospitalization [HFH], heart transplantation [HTx], and malignant ventricular arrhythmias [MVA]) in genotype-negative and genotype-positive men and women (left), and stratified by genogroup (right). **B**, Unadjusted 5-year risk of MVA in genotype-negative and genotype-positive men and women (left), and stratified by genogroup (right). Estimates are derived from Kaplan-Meier survival curves.

attributed to patients with DCM due to a pathogenic/LP variant in nuclear envelope, cytoskeletal/Z-disk, and desmosomal genes. This observation is in line with previous literature showing that the clinical course differs depending on the underlying affected gene.[18,20] The nuclear envelope genogroup was strongly enriched with patients carrying a *LMNA* variant (91%). Men with DCM due to a pathogenic/LP variant in *LMNA* have a worst prognosis due to higher prevalence of MVAs and end-stage heart failure.[21] Male sex is therefore one of the clinical parameters that is incorporated in the risk prediction model for ventricular arrhythmias in patients with *LMNA* variants.[8] Sex is an important factor to take into consideration when developing gene-specific risk prediction models. In addition, we found that men with DCM due to pathogenic/LP variants in cytoskeletal/Z-disk, desmosomal, and nuclear envelope genes also have a worse prognosis for MVA compared with patients with DCM and no genetic variant. These groups are strongly enriched by patients with a *FLNC* and *DSP* variant and pathogenic variants in these genes are associated with MVA.[22,23] While the effects on outcome in men with DCM was depended on underlying affected gene, this effect was less definite in women. Cytoskeletal/Z-disk, desmosomal, and nuclear envelope genes have a similar risk for MVA compared with genotype-negative women. To provide specific recommendations per sex and rare genotype, gene-specific studies examining sex differences is warranted. Future studies should focus on including large sample sizes of women with a pathogenic/LP variant. Moreover, future research should explore the differences in diagnosis rates between men and women with genetic DCM, a disease with a dominant inheritance pattern that should effect men and women equally. This unequal distribution could be due to biological differences in sex-specific disease modulators or because of societal biases in inclusion of men and women within DCM registries.

Genotype-specific differences in LVEF after 1-year follow-up and the rate of LVRR were noted in women with DCM but not in men with DCM. While the increased prevalence of LVRR in patients with DCM due to TTNtv

is well described,[24] the low rate in women with DCM due to desmosomal variants is less well recognized. Understanding how LVEF recovery varies by sex and genotype, as indicated by genotype-specific differences observed in patients with DCM, allows for a more personalized therapeutic approach. For instance, patients with significant improvement may see a modification in their medication regimen or reconsideration of the need for device therapy.

Since we did not observe a difference in baseline characteristics (age, LVEF, NYHA class) and medical therapy, other factors might play an important role in the observed sex- and genotype differences in outcome and cardiac function. Future research should focus on other factors beyond therapy, like lifestyle (ie, alcohol consumption), comorbidities (ie, diabetes), and sex-specific factors (ie, reproductive factors and hormonal changes) that could influence prognosis in a sex-specific manner.

Clinical Outlook and Future Perspectives

Genetic testing is an important strategy for identifying individuals at risk.[25,26] Clinical practitioners should take genotype and sex into account when treating patients with DCM since both genotype and sex have effects on long-term follow-up.[8,21–23] Although we did not found a significant interaction between sex and genotype on outcome, the current guidelines include gene-specific risk prediction models to support device implantation that do include sex.[15,27,28] It is likely that the interaction between gene variant and sex is more complex and should be analyzed within gene-specific risk analyses. We and others observed interesting differences in disease development and outcome that could form the base for future studies. For example, of observations that deserve further research, include, (1) treatments can be tailored based on the likelihood of LVEF improvement, considering factors such as the patients' sex and specific genetic background, and (2) the observed unfavorable trend for major arrhythmias in women with cytoskeletal, desmosomal, and nuclear envelope variants who could benefit equally from device therapy as currently recommended for men. Nonetheless, due to the historical underrepresentation of women in clinical trials, there is a significant gap in data on the most effective treatment strategies for women with DCM, a shortfall highlighted by the American Heart Association's scientific statement on DCM.[29]

Limitations

A limitation of this study is the potential for survivorship bias. In this study we did not had the clinical presentation as a variable that we could use as a surrogate. Therefore patients could have been enrolled at different stages of disease, independent of sex or genotype. As such, survival outcomes may reflect both biological factors and differences in health care access or timing of diagnosis and cautious interpretation of survival differences is recommended.

The current study was conducted in 4 tertiary referral centers. Consequently, the included patients in this study might not completely represent the entire DCM spectrum and these results should only be extrapolated to similar cohorts. We noted differences in baseline characteristics per participating center that are partially explained by geographic differences and variation in health care policies by country.

Acknowledging the retrospective design of our study, we understand the potential for sampling bias, which may contribute to the disproportionate representation of men in our cohort, a phenomenon similarly reported in other studies.[12,30] While the predominance of men in DCM cohorts is widely recognized, we concede that such oversampling in cardiomyopathy registries is frequently observed and could be indicative of an under-recognition or under-diagnosis of the disease among women.

Due to the limited number of specific gene carriers, patients were clustered into functional gene groups, therefore we could not perform a gene-specific analysis with sufficient statistical power. Therefore subtle gene-specific interactions with sex may therefore be missed. As the proportion of women with DCM and a pathogenic gene variant is lower in all centers compared with men, the number of women with DCM per genogroup remained small, which could potentially explain the nonsignificant results observed in women with DCM and genetic variants. Information regarding age of menopause onset was not available.

Finally, data on guideline-directed medical therapy at diagnosis were collected but these variables were not included in the outcome analyses due to potential overfitting of the model, and incomplete data on uptitration of medication over time.

Conclusions

Men with a pathogenic/LP variant have the worst prognosis, showing an increased risk for major adverse events and malignant ventricular arrhythmias. In addition, the occurrence of adverse events during long-term follow-up varies per specific underlying affected gene in male patients with DCM. Genetic architecture and sex are important predictors of clinical prognosis in DCM and should be considered in individualized risk prediction.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S5
Figures S1–S4

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