

ORIGINAL RESEARCH ARTICLE



Left Ventricular Hypertrabeculation and Prognosis in Dilated Cardiomyopathy

Nerea Mora-Ayestarán¹, MD*; Noemi Ramos-Lopez², MD*; Juan Pablo Ochoa³, MD, PhD; Amaia Yuan Ibargoyen⁴, MD; Eduard Claver-Garrido, MD, PhD; Cristina Gómez-González, MD; Ahmad S. Amin⁵, MD, PhD; María Gallego-Delgado⁶, MD, PhD; Guillem Casas-Masnou⁷, MD, PhD; Marina Navarro-Peñalver⁸, MD, PhD; Jose María Larrañaga-Moreira⁹, MD; José Manuel García-Pinilla, MD, PhD; Francisco J. Bermudez-Jimenez¹⁰, MD, PhD; María Victoria Mogollón-Jiménez¹¹, MD; Gonzalo Cabezón-Villalba¹², MD, PhD; Antoni Bayes-Genis¹³, MD, PhD; Vicente Climent-Payá¹⁴, MD, PhD; Rafael Salguero-Bodes¹⁵, MD; Ana García-Álvarez¹⁶, MD, PhD; María Brion¹⁷, PhD; Ramon Brugada¹⁸, MD, PhD; Esther Zorio¹⁹, MD, PhD; Tomas Ripoll-Vera²⁰, MD, PhD; María Luisa Peña-Peña²¹, MD, PhD; Ana Royuela²², PhD; Miriam Sánchez²³, MD; Carles Díez-Lopez²⁴, MD, PhD; Elena Rodríguez González²⁵, MD, PhD; Edwin Poel²⁶, MSc; Eduardo Villacorta²⁷, MD, PhD; Javier Limeres-Freire²⁸, MD, PhD; María Sabater-Molina²⁹, PhD; Roberto Barriales-Villa³⁰, MD, PhD; Gemma Lacuey-Lecumberri³¹, MD, PhD; Andrea Di Marco³², MD, PhD; María Angeles Espinosa-Castro³³, MD, PhD; Connie R. Bezzina³⁴, PhD; José F. Rodríguez-Palomares, MD, PhD; María Teresa Basurte-Elorz³⁵, MD; Jesus G. Mirelis, MD, PhD†; Pablo Garcia-Pavia³⁶, MD, PhD†

BACKGROUND: Left ventricular (LV) hypertrabeculation, formerly termed LV noncompaction, is a heterogeneous myocardial entity linked to adverse cardiovascular outcomes. This study evaluated embolic risk in patients with dilated cardiomyopathy (DCM) according to the presence of hypertrabeculation and examined its prevalence and prognostic relevance across DCM genotypes.

METHODS: Clinical data from 1160 patients with DCM evaluated by cardiac magnetic resonance imaging and genetic testing (n=997 [86%]) were collected from 22 international centers. End points included embolic events, advanced heart failure events, and major ventricular arrhythmias.

RESULTS: LV hypertrabeculation was identified in 354 patients (30.5%) by fractal analysis and in 343 (29.7%) according to Petersen criteria, with good concordance. After a median follow-up of 5.1 years (interquartile range, 2.8–7.4), embolic events occurred in 37 patients (3.2%), advanced heart failure in 62 (5.3%), and major ventricular arrhythmias in 136 (11.7%). Hypertrabeculation was not associated with increased embolic risk (hazard ratio, 1.5 [95% CI, 0.75–3.00]), even among patients in sinus rhythm with LV ejection fraction $\leq 40\%$ (hazard ratio, 1.89 [95% CI, 0.7–5.5]). In contrast, atrial fibrillation and reduced LV ejection fraction were associated with embolic events (both $P < 0.01$). LV hypertrabeculation was not associated with an increased risk of major ventricular arrhythmias or advanced heart failure; genotype, LV ejection fraction, and late gadolinium enhancement emerged as the main predictors of adverse outcomes. The prevalence of LV hypertrabeculation varied across genotypes, with the highest prevalence observed in patients with sequence variants in motor sarcomeric genes (58%), *TTN* (38%), and genotype-negative status (33%), and the lowest prevalence observed among those with variants in cytoskeletal/Z-disk (7%) and nuclear envelope (5%) genes. Hypertrabeculation was not associated with adverse outcomes within any genotype.

CONCLUSIONS: Although LV hypertrabeculation is common in DCM, it is not associated with worse outcomes and should not prompt differential clinical management. The embolic risk in patients with DCM and hypertrabeculation is low, including in those with reduced LV ejection fraction without atrial fibrillation, and does not support prophylactic anticoagulation in these patients.

Key Words: cardiomyopathy ■ dilated ■ embolism ■ genes ■ prognosis

Correspondence to: Jesus G. Mirelis, MD, PhD, or Pablo Garcia-Pavia, MD, PhD, Department of Cardiology, Hospital Universitario Puerta de Hierro, Manuel de Falla, 2, Majadahonda, Madrid, 28222, Spain. Email jesusgmirelis@telefonica.net or pablogpavia@yahoo.es

*N. Mora-Ayestarán and N. Ramos-Lopez contributed equally.

†J.G. Mirelis and P. Garcia-Pavia contributed equally.

This manuscript was handled and accepted by the editorial team led by Dr Joseph Hill.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.125.078536>.

© 2026 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, LLC. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In a large, contemporary, genotyped dilated cardiomyopathy cohort evaluated with cardiac magnetic resonance imaging, left ventricular hypertrabeculation is common ($\approx 30\%$), but not associated with disease severity or adverse clinical outcomes.
- The prevalence of hypertrabeculation varies across genotypes, but does not confer increased risk within any genotype.
- Hypertrabeculation is not associated with embolic risk in patients with dilated cardiomyopathy, including those in sinus rhythm with severe systolic dysfunction.

What Are the Clinical Implications?

- The low embolic risk observed does not support routine anticoagulation in patients with dilated cardiomyopathy with hypertrabeculation, including those with left ventricular ejection fraction $\leq 40\%$.
- Within the dilated cardiomyopathy spectrum, left ventricular hypertrabeculation should be regarded as a phenotypic trait associated with certain genotypes and should not prompt changes in therapeutic management or surveillance.

Left ventricular (LV) hypertrabeculation, previously termed LV noncompaction, is a heterogeneous entity characterized by prominent LV trabeculae, deep intertrabecular recesses, and a thin, compacted myocardial layer.¹

LV hypertrabeculation historically has been associated with a high risk of heart failure (HF), ventricular arrhythmias, embolic events, and mortality, leading to more aggressive use of certain therapies. The high thromboembolic risk reported in early series has led some groups to recommend anticoagulation in patients with LV hypertrabeculation and reduced ejection fraction (LV ejection fraction [LVEF] $\leq 40\%$) in the absence of atrial fibrillation (AF) or other indications.^{2–4}

Nonetheless, recent advances in cardiac imaging, particularly the widespread adoption of cardiac magnetic resonance imaging (CMR), have led to a substantial increase in the detection of hypertrabeculation. This newly recognized high prevalence has raised important questions about the prognostic value of hypertrabeculation and sparked concerns regarding potential overdiagnosis and overtreatment. Despite its increasing recognition, LV hypertrabeculation in the setting of dilated cardiomyopathy (DCM) remains a poorly defined entity with uncertain clinical and prognostic significance.

We evaluated embolic risk in patients with DCM according to the presence of hypertrabeculation and

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AHF	advanced heart failure
CMR	cardiac magnetic resonance imaging
DCM	dilated cardiomyopathy
FD	fractal dimension
HF	heart failure
HR	hazard ratio
IQR	interquartile range
LGE	late gadolinium enhancement
LV	left ventricular
LVEF	left ventricular ejection fraction
MVA	major ventricular arrhythmia
NYHA	New York Heart Association

assessed the prevalence and prognostic impact of hypertrabeculation in a contemporary cohort of patients with genetically characterized DCM evaluated by CMR.

METHODS

Study Design

This is an international, multicenter, retrospective, observational, and longitudinal study of consecutive patients with DCM evaluated by CMR and recruited from 22 European hospitals from The Netherlands and Spain. DCM was defined as the presence of LVEF $< 50\%$ on CMR in the absence of abnormal loading conditions, coronary artery disease (by coronary angiography or computed tomography), excessive alcohol consumption, or any other identifiable cause.⁵ The study was approved by the Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Helsinki Declaration. The authors from each participating center guarantee the integrity of data.

Participants

Participating individuals were consecutive patients with non-ischemic DCM who underwent CMR between 2003 and 2023 at participating centers. Genetic testing was conducted according to local practice and results were collected if they fulfilled the study requirements. Genetic testing was performed using targeted next-generation sequencing panels including > 50 cardiomyopathy-associated genes in probands, or by Sanger sequencing to detect known pathogenic or likely pathogenic variants previously identified in family members with DCM. Genetic testing was performed at participating institutions or an accredited genetics laboratory. CMR studies and genetic testing results were centrally evaluated at the coordinating center by experts in genetics and CMR.

Clinical outcomes were ascertained through systematic review of electronic medical records at each participating center, including hospital discharge summaries, outpatient clinical documentation, and, when available, device interrogation reports. Events were defined according to prespecified criteria,

and all outcomes were independently adjudicated by investigators blinded to hypertrabeculation status.

Demographics, symptoms, and 12-lead ECG data were collected from clinical records at each participating center using uniform methodology. DCM was classified as familial if at least 1 relative in addition to the proband had DCM during life or at postmortem examination. Sporadic DCM was defined by the absence of a family history of DCM and no evidence of DCM in relatives who underwent screening. Infiltrative cardiomyopathies were excluded if the phenotype was suggestive.

Cardiac Magnetic Resonance

Patients underwent CMR on 1.5 or 3.0 T magnetic resonance scanners. Steady-state free precession cine images were acquired in short-axis and long-axis views. Late gadolinium enhancement (LGE) images were obtained using a segmented inversion-recovery gradient-echo technique in long- and short-axis images 10 to 15 minutes after intravenous administration of 0.15 mmol/kg gadolinium contrast. Inversion time was adjusted to null the signal from normal myocardium.

Images from all centers were analyzed centrally by 2 CMR experts (N.R.-L., G.C.-M.) blinded to genotype and outcomes using dedicated software (cvi42; Circle Cardiovascular Imaging Inc). Disagreements were resolved by consensus, with adjudication by a senior expert (J.G.M.) when necessary. LV volume, LV mass, and LVEF were measured from short-axis cine stacks using standard methods⁶ and the presence of LGE was assessed visually. A total of 34 patients were excluded due to CMR studies with poor image quality that made fractal analysis unfeasible.

Assessment of LV Hypertrabeculation by CMR

LV hypertrabeculation was assessed using 2 methods: the Petersen ratio and fractal dimension (FD) analysis (Figure 1).

For the primary analysis of the study, patients were considered to have hypertrabeculation based on the FD criterion. A secondary analysis was performed according to the Petersen criterion.

For the identification of LV hypertrabeculation using the Petersen method, all segments (excluding segment 17) were evaluated on end-diastolic cine CMR images in the 3 standard long-axis views. A noncompacted/compacted ratio >2.3 was considered diagnostic for LV hypertrabeculation, as described by Petersen et al.⁷ FD analysis was performed using a prototype version of cvi42 software (version 6.0), a semiautomatic tool to quantify the degree of hypertrabeculation. An apical maximum FD ≥ 1.30 was considered diagnostic for LV hypertrabeculation, based on criteria previously proposed by Captur et al.⁸ Details about the technical specifications of fractal analysis and the Petersen criterion are provided in the [Supplemental Material](#).

Genotype

Genetic variants were centrally classified as positive (pathogenic or likely pathogenic variant), inconclusive (variants of uncertain significance that could not be excluded as potentially contributing to the development of the phenotype), or negative (no genetic variant, benign or likely benign variants, or variants of uncertain significance not associated with the phenotype). Classification was performed through a systematic review by a cardiologist specialized in cardiovascular genetics (J.P.O.) using modified criteria from the American College of Medical Genetics and Genomics,⁹ as detailed in the [Supplemental Material](#).

To assess the impact of hypertrabeculation within specific genetic subgroups, genes were clustered into functional categories based on shared biologic roles, involvement in common cellular processes, subcellular localization, and other properties

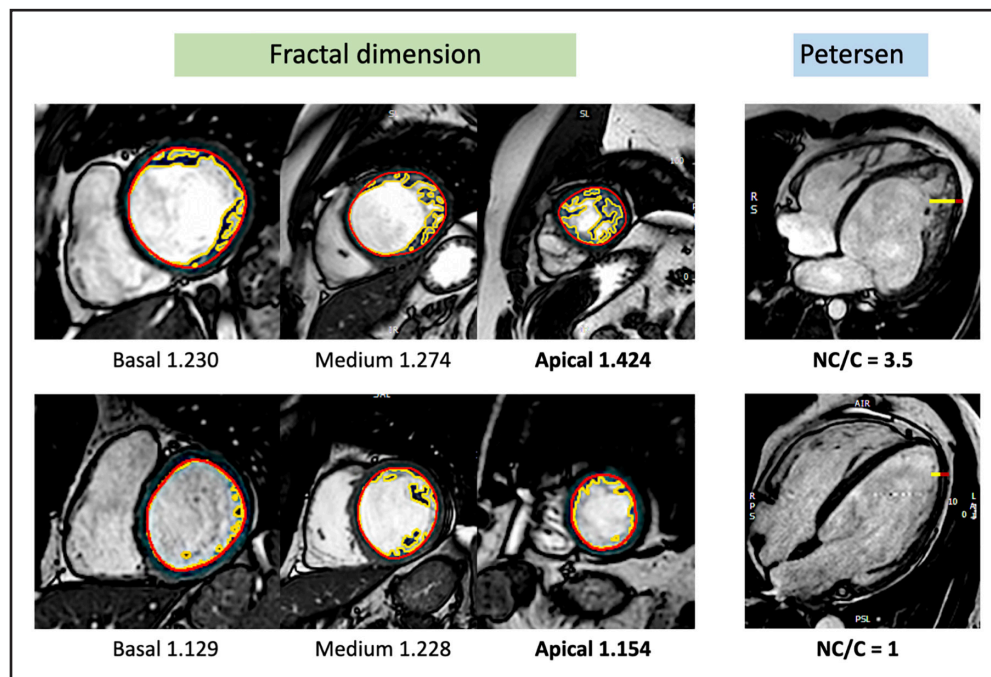


Figure 1. Assessment of hypertrabeculation by fractal analysis and the Petersen method.

NC/C indicates noncompacted/compacted ratio.

supported by consolidated evidence from the literature and biologic databases.¹⁰ Due to its high prevalence and unique characteristics in DCM, *TTN* was considered as a separate category. The functional gene groups included (1) structural cytoskeleton/Z-disk, (2) desmosomal, (3) nuclear envelope, (4) motor sarcomeric, (5) *TTN*, and (6) other genes. To ensure a conservative analytic approach, individuals with inconclusive results ($n=93$ [8.0%]) and those harboring >1 pathogenic or likely pathogenic variant ($n=6$ [0.52%]) were excluded from the functional gene group analysis. In addition, a gene-specific subanalysis was performed for DCM-causing genes with at least 10 individuals harboring DCM-causing variants in the cohort.

Outcomes

The primary end point was the occurrence of embolic events, according to the presence or absence of LV hypertrabeculation. Embolic events were defined as clinically documented thromboembolic events, including ischemic stroke, transient ischemic attack, or systemic embolism.

Secondary end points included the prevalence of hypertrabeculation across genetic subgroups and the association of hypertrabeculation with advanced HF (AHF) and major ventricular arrhythmias (MVA). The AHF end point included ventricular assist device implantation for refractory HF, heart transplant, and AHF-related mortality. AHF-related mortality was defined as death occurring in the context of advanced HF, based on review of the medical records and adjudicated by the study investigators. MVA included sudden cardiac death or aborted sudden cardiac death, sustained ventricular tachycardia, and appropriate implantable cardioverter defibrillator interventions. Only appropriate implantable cardioverter defibrillator shocks to terminate ventricular tachycardia or ventricular fibrillation episodes were considered for the purpose of this study (antitachycardia pacing therapy was not considered).

Patients had planned reviews at participating centers every 6 to 12 months or more frequently if clinically indicated. The follow-up for each patient was calculated from the date of their CMR study to the occurrence of a study end point, death from another cause, or the date of their last evaluation.

Statistics

Continuous variables are expressed as mean $\pm$ SD or median (interquartile range [IQR]), as appropriate. Linearity of continuous covariates was assessed before model fitting. When evidence of nonlinearity was observed, restricted cubic splines were used. Groups were compared using Student *t* test or the Mann-Whitney *U* test, or 1-way ANOVA or the Kruskal-Wallis test when comparing >2 groups. Categorical variables are expressed as counts (percentages) and were compared using the Pearson χ^2 or Fisher exact test, as appropriate. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compare them. Median follow-up was estimated through the reverse Kaplan-Meier method.

The associations between hypertrabeculation and MVA and AHF were assessed using standard Cox proportional hazards models with an unspecified baseline hazard, with hypertrabeculation as the primary variable of interest. These models were adjusted for genotype, LVEF, New York Heart Association

(NYHA) functional class, and LGE, based on established clinical relevance for arrhythmic and HF outcomes.

For embolic events, an extended Cox proportional hazards model was used, with AF included as a time-dependent covariate. Patients contributed person-time as no AF until the date of first documented AF occurrence and as AF-positive thereafter. Follow-up time was measured from the baseline cardiac magnetic resonance date, and AF onset corresponded to the first documented diagnosis (ECG, Holter monitoring, or medical record documentation) during follow-up. The model was also adjusted for anticoagulation status and LVEF, as these variables represent the core established determinants of embolic risk. Other covariates with less consistent evidence of association were not included to avoid overparameterization given the limited number of observed events. Hazard ratios (HRs) along with the corresponding 95% CIs were estimated. In all Cox analyses, proportional hazards assumption was assessed using Schoenfeld residuals.

To assess agreement between the fractal method and the Petersen criterion in detecting LV hypertrabeculation, Cohen kappa coefficient was calculated. Analyses were conducted using Stata Statistics version 18 (StataCorp). Two-tailed *P* values <0.05 were considered statistically significant.

Data Sharing

Qualified researchers may submit a request containing the research objectives, end points or outcomes of interest, a statistical analysis plan, data requirements, a publication plan, and qualifications of the researchers. Requests will be reviewed by the corresponding authors. If approved, information necessary to address the research question will be provided under the terms of a data sharing agreement. Requests may be submitted to the corresponding authors.

RESULTS

Characteristics of the Patients

A total of 1160 patients met inclusion criteria, 978 of whom (84.4%) were unrelated index cases and 181 (15.6%) were relatives. Characteristics of the patients are presented in Table 1. Most patients were men (65.3%). The median age at CMR was 55.5 years (IQR, 44.7–65.9 years), and most patients were classified as NYHA functional class I or II (76.4%) at baseline. The prevalence of AF was 15.0%; left bundle branch block was present in 29.9% and low voltages on limb leads were found in 12.2%.

The median LVEF at baseline CMR was 36% (IQR, 26%–44%), and LGE was present in 354 individuals (31.0%). LV volume was 121.3 mL/m² (IQR, 100.9–147.0 mL/m²), with a median LV mass of 70.3 g/m² (IQR, 58.0–82.9 g/m²). Left atrial indexed volumes were enlarged to 46.0 mL/m² (IQR, 34.1–62.8 mL/m²), whereas the measurements of the right atrium and right ventricle were largely within normal limits.

Regarding baseline medical treatment, 79.3% of patients were treated with β -blockers; 82.1% with an

Table 1. Characteristics According to Left Ventricular Hypertrabeculation

Characteristics	Total (n=1160)	No hypertrabeculation (n=806)	Hypertrabeculation (n=354)	P value
Demographics				
Male	757 (65.26)	523 (64.89)	234 (66.10)	0.689
Proband	978 (84.38)	674 (83.73)	304 (85.88)	0.353
Age, y	55.54 (44.69–65.94)	56.40 (46.03–66.01)	54.13 (40.72–65.86)	0.038
White patients	1106 (98.05)	765 (97.83)	341 (98.55)	0.549
FH of DCM	445 (40.49)	318 (41.90)	127 (37.35)	0.156
FH of SCD, first-degree relative	112 (10.06)	75 (9.77)	37 (10.72)	0.623
FH of SCD, non–first-degree relative	186 (16.85)	135 (17.74)	51 (14.87)	0.238
Skeletal myopathy	25 (2.41)	15 (2.12)	10 (3.03)	0.372
Previous recovered SCD	31 (2.67)	22 (2.73)	9 (2.54)	0.856
Hypertension	402 (34.66)	290 (35.98)	112 (31.64)	0.152
Dyslipidemia	375 (32.33)	268 (33.25)	107 (30.23)	0.310
Diabetes	192 (16.55)	135 (16.75)	57 (16.10)	0.785
NYHA functional class at first evaluation				
I	468 (42.12)	303 (39.87)	165 (47.01)	0.160
II	381 (34.29)	273 (35.92)	108 (30.77)	
III	225 (20.25)	158 (20.79)	67 (19.09)	
IV	37 (3.33)	26 (3.42)	11 (3.13)	
Baseline ECG				
Atrial fibrillation or flutter	174 (15.00)	134 (16.63)	40 (11.30)	0.019
QRS duration, mm	106 (92–140)	106 (91–140)	105 (92–140)	0.753
LBBB	343 (29.88)	230 (28.89)	113 (32.10)	0.274
Low QRS voltage limb leads	128 (12.18)	94 (13.24)	34 (9.97)	0.129
Baseline CMR				
NC/C ratio	1.9 (1.4–2.5)	1.7 (1.2–2)	2.7 (2.3–3.2)	<0.001
LGE	354 (31.00)	269 (33.71)	85 (24.71)	0.003
LVEF, %	36.15 (26.10–44.34)	34.85 (25.63–43.91)	38.19 (27.5–45.21)	0.015
LVEDV, mL	228 (188.2–286)	234.2 (190–289.8)	217.75 (176.8–274.8)	0.003
LV mass, g	133 (108.2–160)	133.75 (109–160)	131 (108–160.5)	0.479
RVEDV, mL	155 (123.8–195)	156 (126.3–200.7)	150.9 (118.6–186)	0.002
RV mass, g	31 (23.9–40.65)	30.1 (23–39.7)	33.6 (25–42.3)	0.005
LA maximum volume, mL	87 (64.6–117)	87.7 (65–119.1)	85 (63–112.5)	0.209
RA maximum volume, mL	67.7 (51.1–91)	69 (52.8–94)	63.15 (48.2–80.65)	<0.001
LVEDV index, mL/m ²	121.3 (100.9–147.0)	123.5 (103.5–148.9)	115.1 (96.9–141.0)	0.004
LV mass index, g/m ²	70.3 (58.0–82.9)	70.3 (58.2–82.4)	70.2 (57.5–83.3)	0.770
RVEDV index, mL/m ²	82.5 (67.7–100.0)	83.9 (68.6–102.5)	79.6 (63.7–95.9)	0.001
RV mass index, g/m ²	16.7 (13.0–21.6)	16.4 (12.5–21.5)	17.7 (13.7–21.8)	0.011
LA maximum volume index, mL/m ²	46.0 (34.1–62.8)	46.6 (35.0–63.1)	45.3 (33.0–61.9)	0.252
RA maximum volume index, mL/m ²	35.5 (27.5–46.4)	36.7 (28.5–47.2)	33.1 (24.7–42.6)	<0.001
Drug treatment at baseline				
β-blocker	919 (79.29)	635 (78.78)	284 (80.45)	0.519
ACEI/ARB/ARNI	951 (82.05)	656 (81.39)	295 (83.57)	0.373
MRA	473 (40.81)	330 (40.94)	143 (40.51)	0.890
SGLT2i	60 (5.18)	43 (5.34)	17 (4.82)	0.710
Ivabradine	77 (6.65)	54 (6.71)	23 (6.52)	0.904
Diuretics	426 (36.85)	303 (37.69)	123 (34.94)	0.374

(Continued)

Table 1. Continued

Characteristics	Total (n=1160)	No hypertrabeculation (n=806)	Hypertrabeculation (n=354)	P value
Anticoagulation	253 (21.81)	168 (20.84)	85 (24.01)	0.229
Aspirin	153 (13.54)	97 (12.39)	56 (16.14)	0.089
Treatment at last evaluation				
β-blocker	942 (87.87)	653 (86.84)	289 (90.31)	0.110
ACEi/ARB/ARNI	964 (90.09)	671 (89.47)	293 (91.56)	0.293
MRA	671 (63.18)	471 (63.31)	200 (62.89)	0.898
SGLT2i	427 (44.02)	311 (45.53)	116 (40.42)	0.143
Ivabradine	106 (9.94)	67 (8.97)	39 (12.23)	0.104
Diuretics	390 (36.76)	295 (39.76)	95 (29.78)	0.002
ICD	376 (32.41)	270 (33.50)	106 (29.94)	0.234
CRT	174 (16.28)	133 (18.27)	41 (12.02)	0.010

Values are n (%); continuous variables are expressed as median (interquartile range). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; DCM, idiopathic dilated cardiomyopathy; FH, family history; HF, heart failure; ICD, implantable cardioverter defibrillator; LA, left atrial; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NC/C, noncompacted/compacted ratio; NYHA, New York Heart Association; RA, right atrial; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotransporter type 2 inhibitor.

angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or angiotensin receptor/neprilysin inhibitor; 40.8% with a mineralocorticoid receptor antagonist; and 5.2% with a sodium-glucose cotransporter type 2 inhibitor. At the last follow-up, 87.9% of patients were receiving β-blockers; 90.1% an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or angiotensin receptor/neprilysin inhibitor; 63.2% a mineralocorticoid receptor antagonist; and 44.0% a sodium-glucose cotransporter type 2 inhibitor. In relation to device therapy, 376 patients (32.4%) received an implantable cardioverter defibrillator during follow-up and 174 (16.3%) a cardiac resynchronization therapy device.

LV Hypertrabeculation

LV hypertrabeculation was identified in 354 patients (30.5%) based on the FD analysis and in 343 patients (29.65%) according to Petersen criteria. An agreement rate of 84.79% was observed between the 2 methods. The Cohen kappa coefficient was 0.638 (95% CI, 0.590–0.687), indicating substantial agreement. Among patients with hypertrabeculation according to the Petersen criterion, the median NC/C ratio was 2.7 (IQR, 2.3–3.2).

Clinical characteristics of patients regarding the presence or absence of LV hypertrabeculation are described in Table 1. Patients with hypertrabeculation were younger (54.1 versus 56.4 years [$P=0.038$]), had higher LVEF (38.2% versus 34.9% [$P=0.015$]), and showed a lower prevalence of LGE (24.7% versus 33.7% [$P=0.003$]) and AF (11.3% versus 16.6% [$P=0.019$]). Regarding treatment, no significant differences were observed in baseline therapy; however, at last follow-up, patients with hypertrabeculation were less frequently receiving diuretics

(29.8% versus 39.8% [$P=0.002$]), and less frequently had cardiac resynchronization therapy (12.0% versus 18.3% [$P=0.010$]), despite similar rates of left bundle branch block at baseline (32.1% versus 28.9% [$P=0.274$]).

Genotype

A DCM-related pathogenic or likely pathogenic disease-causing variant was identified in 329 individuals (28.4%) in the cohort. A complete list of the disease-causing variants can be found in the [Supplemental Material](#).

Among the 329 individuals with 1 pathogenic or likely pathogenic variant, the most frequently involved gene was *TTN*, identified in 122 individuals (37.1%), followed by *DSP* (n=31 [9.4%]), *FLNC* (n=28 [8.5%]), *BAG3* (n=23 [7.0%]), *MYH7* (n=21 [6.4%]), *LMNA* (n=20 [6.1%]), and *RBM20* (n=17 [5.2%]). The distribution of genes according to the functional gene group is listed in [Table S1](#).

Outcomes

After a median follow-up of 5.10 years (IQR, 2.77–7.44 years), embolic events occurred in 37 patients (3.2%), AHF in 62 (5.3%) and MVA in 136 (11.7%). The incidence rates were 0.55, 0.94, and 2.03 per 100 person-years, respectively (Table 2).

Event rates during follow-up according to the presence of hypertrabeculation are presented in [Table S2](#) (FD criterion) and [Table S3](#) (Petersen criterion).

Hypertrabeculation and Embolic Events

A total of 13 patients with hypertrabeculation (3.7%) had embolic events, compared with 24 (3.0%) without hypertrabeculation. Incidence rates were 0.6 and 0.5 per 100

patient-years in the nonhypertrabeculated and hypertrabeculated DCM groups, respectively ($P=0.730$). Of the 37 patients with embolic events, 15 (40.5%) had documented AF or atrial flutter before the event, and in 6 additional patients (16.2%), AF was first identified at the time of the embolic event or within the following 6 months.

In multivariable analysis, hypertrabeculation did not show association with an increased risk of embolism (HR, 1.50 [95% CI, 0.75–3.00]; $P=0.249$), whereas the presence of AF or atrial flutter (HR, 3.26 [95% CI, 1.47–7.23]; $P=0.004$) and lower LVEF (HR, 1.04 per 1% decrease [95% CI, 1.01–1.08]; $P=0.005$) were associated with embolic events (Table 3 and Table S6).

Embolism Risk in Patients with LVEF $\leq 40\%$ and Sinus Rhythm

Among the 1160 patients included in the study, 174 (15.0%) had a history of AF or atrial flutter, 109 (11.1%) were receiving anticoagulation therapy for other indications, and 466 (40.2%) had LVEF $>40\%$. Among the 496 patients in sinus rhythm, not receiving anticoagulation, and with LVEF $\leq 40\%$, 14 patients (2.8%) experienced embolic events during follow-up. These events occurred in 8 patients (2.2%) without hypertrabeculation and in 6 patients (4.4%) with hypertrabeculation ($P=0.205$). Among patients in sinus rhythm with LVEF $\leq 40\%$, the presence of hypertrabeculation did not show association with embolic events (HR, 1.89 [95% CI, 0.66–5.46]).

Hypertrabeculation and MVA

MVA occurred in 103 patients (12.8%) without hypertrabeculation and in 33 patients (9.3%) with hypertrabeculation. Patients with hypertrabeculation showed a lower incidence of MVA compared with those without hypertrabeculation (log-rank 0.036; Figure 2A).

The HR for MVA regarding the presence of hypertrabeculation was 0.64 (95% CI, 0.42–0.97; $P=0.037$). However, in the multivariable analysis (adjusted for genotype, LGE, NYHA functional class, and LVEF), hypertrabeculation lost the association with the occurrence of arrhythmic events (HR, 0.93 [95% CI, 0.59–1.48]; $P=0.769$).

In the multivariable analysis, carrying a variant in nuclear envelope genes was associated with MVA (HR, 4.4 [95% CI, 2.0–9.8]), along with LGE (HR, 3.1 [95% CI, 2.1–4.8]) and lower LVEF (HR, 1.03 [95% CI, 1.01–1.05]; Tables S4 and S7).

Hypertrabeculation and AHF

AHF events occurred in 49 patients (6.1%) without hypertrabeculation and in 13 patients (3.7%) with hypertrabeculation. Patients with hypertrabeculation showed a lower incidence of AHF compared with those without hypertrabeculation (log-rank 0.046; Figure 2B).

The HR for AHF regarding the presence of hypertrabeculation was 0.54 (95% CI, 0.29–0.99; $P=0.049$). However, in the multivariable analysis (adjusted by genotype, LGE, NYHA functional class, and LVEF), hypertrabeculation was not associated with AHF (HR, 0.82 [95% CI, 0.43–1.57]; $P=0.550$), whereas the remaining variables were (Tables S5 and S8).

Association Among Hypertrabeculation, Genotype, and Outcomes

Hypertrabeculation varied across functional genetic groups. By gene group, patients with variants in motor sarcomeric genes showed the highest prevalence of hypertrabeculation (30 of 53 individuals [56.6%]), followed by those with *TTN* variants (46 of 122 [37.7%]) and genotype-negative individuals (186 of 567 [32.8%]). In contrast, hypertrabeculation was rare among patients with variants in nuclear envelope genes (1 of 20 [5.0%]) and cytoskeleton/Z-disk genes (3 of 41 [7.3%]). When considering individual genes, the genes most frequently associated with hypertrabeculation were *MYH7* (15 of 21 individuals [71.4%]) and *MYBPC3* (6 of 11 [54.6%]), whereas hypertrabeculation was uncommon in *LMNA* (1 of 20 [5.0%]) and *FLNC* (2 of 28 [7.1%]). The prevalence of hypertrabeculation across the different genetic groups and individual genes are summarized in Figure 3, Table S9, and Figure S2.

Although hypertrabeculation differed between functional genetic groups, the presence of hypertrabeculation was not associated with an increased risk of AHF, MVA, or embolic events within any genotype, suggesting again that the presence of hypertrabeculation does not entail prognostic significance (Table 4).

DISCUSSION

In this large international multicenter cohort of patients with DCM evaluated by CMR, we found that hypertrabeculation was a common finding that did not correlate

Table 2. Incidence Rates of Events According to Hypertrabeculation

Events	Total (n=1160)	No hypertrabeculation (n=806)	Hypertrabeculation (n=354)	P value
Embolism	0.55 (0.39–0.76)	0.51 (0.34–0.77)	0.61 (0.36–1.06)	0.730
Composite MVA	2.03 (1.70–2.42)	2.30 (1.88–2.81)	1.47 (1.02–2.11)	0.036
Composite AHF	0.94 (0.73–1.20)	1.10 (0.83–1.45)	0.60 (0.35–1.04)	0.046

Incidence rates are reported as events per 100 patient-years (95% CI). AHF indicates advanced heart failure; and MVA, major ventricular arrhythmias.

Table 3. Univariate and Multivariable Cox Analysis of Factors Associated With Embolic Events

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Hypertrabeculation	1.21 (0.61–2.39)	0.588	1.50 (0.75–3.00)	0.249
Atrial fibrillation	2.98 (1.53–5.79)	0.001	3.26 (1.47–7.23)	0.004
Anticoagulation at baseline*	1.87 (0.93–3.74)	0.077	0.80 (0.35–1.84)	0.601
Left ventricular ejection fraction†	1.04 (1.01–1.07)	0.004	1.04 (1.01–1.08)	0.005

*Atrial fibrillation was analyzed as a time-dependent variable.
†Per 1% decrease.

with disease severity and was not associated with a worse prognosis. Of note, patients with DCM with hypertrabeculation did not exhibit increased embolic risk, including those with severe systolic dysfunction without AF, not supporting prophylactic anticoagulation in these patients. Moreover, our study shows that prevalence

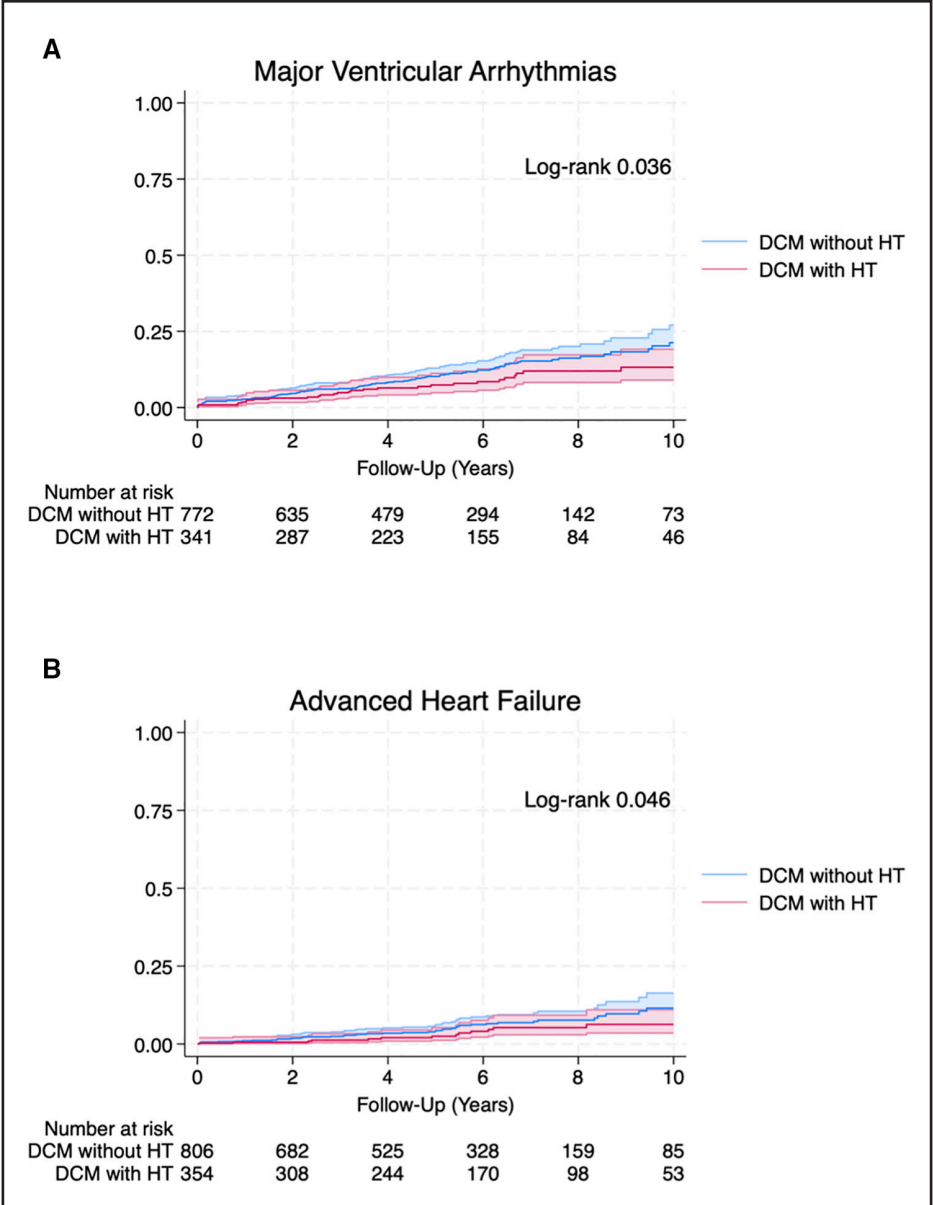


Figure 2. Kaplan-Meier curves for major ventricular arrhythmias and advanced heart failure according to left ventricular hypertrabeculation.
A, Major ventricular arrhythmias. **B**, Advanced heart failure. DCM indicates dilated cardiomyopathy; and HT, hypertrabeculation.

of hypertrabeculation varied across functional genetic groups, with no association between its presence and an increased risk of events within any specific genetic subgroup. Furthermore, prognosis in these patients was primarily determined by genotype, LVEF, and the presence of LGE, whereas hypertrabeculation was not associated with adverse outcomes. Overall, these findings support hypertrabeculation as a phenotypic trait within the DCM spectrum rather than a distinct cardiomyopathy and highlight that the presence of hypertrabeculation in patients with DCM should not modify their therapy and follow-up.

Hypertrabeculation and Thromboembolic Risk

Treatment recommendations for patients with hypertrabeculation with impaired LVEF mirror those for DCM, with the exception of anticoagulation, which is often advised based on older, small-scale studies suggesting an elevated thromboembolic risk.²⁻⁴

This approach is partly driven by the known hypercoagulable state in patients with HF, which increases the risk of thromboembolic events.¹¹ In addition, LV hypertrabeculation has been suggested to carry an intrinsic embolic risk, potentially due to blood stasis within the intertrabecular recesses, which may lead to intraventricular thrombus formation. Notably, an increased prevalence

of AF has been reported among patients with LV hypertrabeculation¹², with reported prevalence reaching 29%,¹³ and increased embolic risk.¹⁴

Early reports of patients with LV hypertrabeculation described a remarkably high incidence of thromboembolic events, with rates reported as high as 29% and 24% in initial studies.^{15,16} More recent and larger series have shown a variable incidence, ranging from 3% to 15%.^{3,17-23} However, these studies are limited by their relatively small sample size and by inclusion of primarily patients referred for echocardiographic assessment. In many cases, the underlying cause of the thromboembolic event was not reported, and key clinical data (such as the presence of concomitant AF or the use of anticoagulant therapy) were frequently absent. Moreover, given the periods during which these studies were conducted, it is likely that a considerable proportion of patients with AF were either not anticoagulated or were receiving solely antiplatelet agents, reflecting common practices of earlier decades. These limitations hinder the accurate assessment of thromboembolic risk in patients with LV hypertrabeculation and highlight the need for contemporary, well-characterized cohorts with comprehensive clinical and therapeutic data.

The current study shows a low incidence of embolic events, with no significant differences between patients

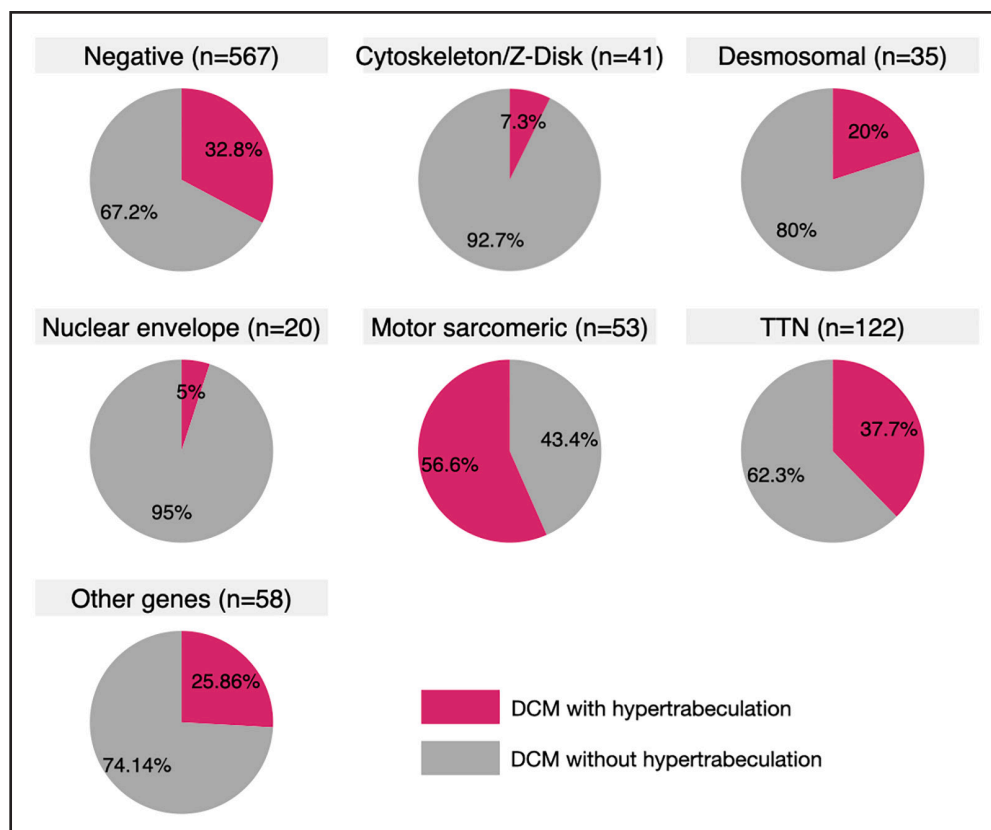


Figure 3. Prevalence of hypertrabeculation according to functional gene group.

DCM indicates dilated cardiomyopathy.

Table 4. Outcomes by Functional Gene Group According to Left Ventricular Hypertrabeculation

Outcomes	Patients	No hypertrabeculation	Hypertrabeculation	P value
Advanced heart failure				
Genotype-negative	567	15/381 (3.94)	7/186 (3.76)	0.920
Cytoskeleton/Z-disk	41	4/38 (10.53)	0/3 (0.00)	1.000
Desmosomal	35	2/28 (7.14)	1/7 (14.29)	0.499
Nuclear envelope	20	3/19 (15.79)	1/1 (100.00)	0.200
Motor sarcomeric	53	2/23 (8.70)	3/30 (10.00)	1.000
TTN	122	8/76 (10.53)	0/46 (0.00)	0.024
Others	58	5/43 (11.63)	1/15 (6.67)	1.000
Malignant ventricular arrhythmias				
Genotype-negative	567	48/381 (12.60)	17/186 (9.14)	0.225
Cytoskeleton/Z-disk	41	5/38 (13.16)	0/3 (0.00)	1.000
Desmosomal	35	8/28 (28.57)	1/7 (14.29)	0.648
Nuclear envelope	20	8/19 (42.11)	1/1 (100.00)	0.450
Motor sarcomeric	53	2/23 (8.70)	5/30 (16.67)	0.685
TTN	122	9/76 (11.84)	4/46 (8.70)	0.765
Others	58	3/43 (6.98)	3/15 (20.00)	0.172
Embolism				
Genotype-negative	567	9/381 (2.36)	8/186 (4.30)	0.204
Cytoskeleton/Z-disk	41	1/38 (2.70)	0/3 (0.00)	1.000
Desmosomal	35	1/28 (3.57)	0/7 (0.00)	1.000
Nuclear envelope	20	1/19 (5.56)	1/1 (100.00)	0.105
Motor sarcomeric	53	1/23 (4.35)	2/30 (6.67)	1.000
TTN	122	3/76 (3.95)	0/46 (0.00)	0.290
Others	58	1/43 (2.33)	0/15 (0.00)	1.000

Values are expressed as n/N (%).

with or without hypertrabeculation. Likewise, prevalence of AF was similar in patients with or without hypertrabeculation. Of note, the AF rate found among patients with hypertrabeculation is consistent with those reported in large contemporary DCM cohorts.^{24,25}

Several clinical trials have evaluated anticoagulation strategies in unselected patients with HF in sinus rhythm. Some studies have shown a reduction in ischemic events,^{26,27} but this benefit was offset by a higher incidence of major bleeding. Therefore, current guidelines do not recommend routine prophylactic anticoagulation in this population.²⁸

In the context of LV hypertrabeculation, the high incidence of embolic events reported in early studies led several authors to recommend long-term prophylactic anticoagulation in all patients with hypertrabeculation and systolic dysfunction, regardless of the presence of intracardiac thrombus or AF. Despite more recent studies reporting lower embolic risk,^{22,23} this recommendation persists in several reviews and clinical guidelines.^{2–4,29} Our findings challenge this recommendation and do not support the use of prophylactic anticoagulation in patients in sinus rhythm based solely on the presence of

hypertrabeculation, even among those with LVEF ≤40%. Given the low embolic risk observed, comparable to that of contemporary DCM cohorts,^{24,25} such a strategy may result in overtreatment without proven benefit and potentially associated with negative side effects.

LV Hypertrabeculation: A Phenotypic Trait or a Distinct Cardiomyopathy?

Advances in cardiac imaging, particularly the widespread use of CMR, have led to increased detection of LV hypertrabeculation in adults,³⁰ with reported prevalence rates of up to 43% in healthy individuals³¹ and up to 36% in patients with DCM.²² In our study, hypertrabeculation was present in ≈30% of patients, using both the Petersen and FD criteria.

Despite its frequent identification, there is no universally accepted gold standard for the diagnosis of LV hypertrabeculation, and there is controversy whether it represents a distinct cardiomyopathy or a phenotypic trait. The American Heart Association classifies LV hypertrabeculation as a primary cardiomyopathy³²; the European Society of Cardiology considers it a phenotypic trait.³³

Diagnosis of LV hypertrabeculation relies primarily on cardiac imaging, with a focus on morphologic criteria that evaluate the relationship between compacted and noncompacted myocardial layers. Among the most commonly used criteria in CMR are the Petersen criteria, which define hypertrabeculation as a noncompacted to compacted myocardial ratio >2.3 at end-diastole.⁷ However, this approach is limited by manual measurement, interobserver variability, and the inability to capture the 3-dimensional complexity of myocardial trabeculation. Fractal analysis has emerged as a more objective and reproducible alternative, providing a quantitative assessment of trabecular complexity.⁸ In the current study, both diagnostic approaches demonstrated good concordance; however, neither showed predictive value for adverse events after adjustment for other well-established prognostic factors and functional measures (LVEF, functional class, LGE, and genotype).

The high prevalence of hypertrabeculation observed in recent studies, combined with its limited prognostic value, challenges its clinical significance and raises concerns about potential overdiagnosis and overtreatment. Although early studies in adults consistently reported a high incidence of ventricular arrhythmias, severe LV dysfunction, advanced HF, embolism, and mortality,^{16,21,34} more recent cohorts have reported conflicting results, often suggesting a more benign course.^{18,35,36}

In our DCM cohort, over a median follow-up of 5.1 years, arrhythmic events occurred in 12% of patients, advanced HF in 5%, and embolic events in 3%, without differences between patients with DCM with or without hypertrabeculation. These results are in line with those of Amzulescu et al,²² who reported an 18% incidence of major adverse cardiac events over 3.4 years among 162 individuals with DCM (58 with hypertrabeculation). In contrast, our findings appear to contrast with previous studies that associated LV hypertrabeculation with increased risk of adverse events,^{37,38} likely due to differences in methodology and lack of adjustment for key clinical variables in these studies.

Previous studies lacked genetic data and most of them did not adjust outcomes for other well-established prognostic factors, such as LVEF or LGE. In our cohort, univariate Cox analysis suggested a lower risk of MVA and AHF in patients with hypertrabeculation; however, this association was lost after multivariable adjustment. Hypertrabeculation did not show association with clinical outcomes and showed no discriminatory capacity for adverse events. In contrast, in the multivariable analysis, AHF events were predicted by genotype, LGE, NYHA functional class, and LVEF, and arrhythmic events were strongly associated with nuclear envelope gene variants, LGE, and LVEF, in line with previous studies in contemporary DCM cohorts.^{39–42}

LV hypertrabeculation is a highly heterogeneous entity that encompasses a broad clinical spectrum. Our data

suggest that the variability observed across different cohorts may be largely attributed to differences in underlying genetic background, which likely influence both the phenotypic expression and clinical outcomes.^{39,40} Specifically, genotypes associated with a worse clinical profile (such as nuclear envelope gene variants, which carry a higher risk of arrhythmias and HF^{39,43}) showed a very low prevalence of hypertrabeculation. In contrast, genotypes with a more favorable prognosis, such as *TTN* and genotype negativity, exhibited a higher prevalence of hypertrabeculation.

Moreover, LV hypertrabeculation is observed in a wide range of physiologic and pathologic contexts (including other cardiomyopathies,⁴⁴ neuromuscular disorders,⁴⁵ congenital heart diseases,⁴⁶ athletic training,^{47,48} and pregnancy⁴⁹), and in healthy individuals,³¹ without evidence of progressive remodeling or adverse outcomes over long-term follow-up.⁵⁰ This supports the notion that LV hypertrabeculation represents a phenotypic trait rather than a distinct pathologic entity. It has also been suggested that hypertrabeculation may be a reactive phenomenon in the context of DCM, in which LV dilation may lead to increased visibility or accentuation of trabeculations, or it may reflect structural remodeling and altered loading conditions of the left ventricle. However, in our study, patients with hypertrabeculated DCM exhibited less remodeled ventricles, with higher LVEF and smaller end-diastolic diameters, not supporting this hypothesis.

Taken together, our data suggest that hypertrabeculation in DCM should be regarded more as a phenotypic trait, rather than as a distinct cardiomyopathy, in line with European Society of Cardiology cardiomyopathy guidelines.³³ This trait appears to be influenced by genetic background and lacks prognostic value.

Clinical Implications

To our knowledge, this is the largest study to assess the prevalence and prognostic impact of LV hypertrabeculation in genotyped patients with DCM evaluated by CMR. Our findings suggest that the presence of hypertrabeculation should not prompt changes in therapeutic management in these patients beyond standard care for DCM.

Accordingly, the low rates of embolic events observed do not support the use of anticoagulation in patients with LV hypertrabeculation with LVEF $\leq 40\%$ who are in sinus rhythm in the absence of other indications.

Limitations

The study's limitations stem from its observational nature and retrospective design. The low event rates found limit statistical power to detect modest differences across patients with or without hypertrabeculation but overall

support that therapeutic decisions in DCM should not be guided by the presence of hypertrabeculation. Gene testing was not uniform and next-generation sequencing genetic testing panels differed among centers and over time, reflecting the evolving understanding of DCM genetics over the past decade. We cannot fully exclude that some patients carrying *MYBPC3* variants included in the study ($n=11$) had end-stage hypertrophic cardiomyopathy. CMR referral was clinically driven across a prolonged study period and multiple sites; therefore, potential referral bias cannot be excluded. Moreover, participating centers are centers specialized in inherited cardiac diseases and HF, which may result in a higher proportion of patients with advanced phenotypes. Therefore, the findings may not be generalizable to other healthcare settings. Although loss to follow-up was minimal, the possibility of incomplete follow-up or nonrandom censoring cannot be excluded. Some technical limitations of fractal analysis include overestimation in the presence of apical thrombus or apical displacement of papillary muscles, which may be misclassified as trabeculae. In addition, hypertrabeculation has been reported to be more prevalent in Black individuals, and the predominantly White composition of our cohort may limit the generalizability of our findings across different racial and ethnic populations.

CONCLUSIONS

Hypertrabeculation is a frequent finding in DCM and appears to vary according to genotype, supporting that LV hypertrabeculation represents a phenotypic trait rather than a distinct cardiomyopathy. In this cohort, hypertrabeculation was not associated with adverse outcomes, suggesting limited prognostic significance and not supporting differential clinical management. The embolic risk of patients with DCM with hypertrabeculation is low and does not support the use of prophylactic anticoagulation, even in patients with severely reduced LVEF.

ARTICLE INFORMATION

Received November 14, 2025; accepted June 5, 2026.

Affiliations

Department of Cardiology, Hospital Universitario Puerta de Hierro, Instituto de Investigación Sanitaria Puerta de Hierro Majadahonda (IDIPHIM), Madrid, Spain (N.M.-A., N.R.-L., J.G.M., P.G.-P.). Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain (N.R.-L., J.P.O., A.G.-Á., P.G.-P.). Department of Cardiology, Área del Corazón, Hospital Universitario de Navarra, Pamplona, Spain (A.Y.I., M.S., G.L.-L., M.T.B.-E.). Department of Cardiology, Hospital Universitari de Bellvitge (E.C.-G., C.D.-L., A.D.), and Bioheart Group, Cardiovascular, Respiratory and Systemic Diseases and Cellular Aging Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL; E.C.-G., C.D.-L., A.D.), l'Hospitalet de Llobregat, Spain. Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain (C.G.-G., E.R.G., M.A.E.-C.). Facultad de Medicina, Universidad Complutense de Madrid, Spain (C.G.-G., E.R.G., M.A.E.-C.). Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain (C.G.-G., E.R.G., M.A.E.-C.). CIBER Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain (C.G.-G., M.G.-D., G.C.-M., M.N.-P., J.M.G.-P., G.C.-V., A.B.-G., R.S.-B., A.G.-Á., M.B., E.Z., E.R.G., E.V., J.L.-F., M.S.-M., R.B.-V., A.D., M.A.E.-C., J.F.R.-P., J.G.M., P.G.-P.). Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Heart Failure & Arrhythmias, Am-

sterdam University Medical Centers, University of Amsterdam, The Netherlands (A.S.A., E.P., C.R.B.). European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD-Heart), Amsterdam, The Netherlands (A.S.A., G.C.-M., M.N.-P., E.P., J.L.-F., C.R.B., J.F.R.-P., J.G.M., P.G.-P.). Department of Cardiology, CSUR Cardiopatías Familiares, Hospital Universitario de Salamanca, Gerencia Regional de Salud de Castilla y León, Salamanca, Spain (M.G.-D., E.V.). Instituto de Investigación Biomédica de Salamanca, Spain (M.G.-D., E.V.). Department of Cardiology, Vall d'Hebron Hospital Universitari (G.C.-M., J.L.-F., J.F.R.-P.), and Cardiovascular Diseases, Vall d'Hebron Institut de Recerca (VHIR; G.C.-M., J.L.-F., J.F.R.-P.), Vall d'Hebron Barcelona Hospital Campus, Spain. Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain (G.C.-M., J.L.-F., J.F.R.-P.). Inherited Cardiac Disease Unit, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain (M.N.-P.). Unidad de Cardiopatías Familiares, Servicio de Cardiología, Complejo Hospitalario Universitario A Coruña, Instituto de Investigación Biomédica de A Coruña, Spain (J.M.L.-M., R.B.-V.). Servicio de Cardiología, Hospital Universitario Virgen de la Victoria, IBIMA-Plataforma BIONAND, Málaga, Spain (J.M.G.-P.). Departamento de Medicina y Dermatología, Universidad de Málaga, Spain (J.M.G.-P.). Servicio de Cardiología, Hospital Universitario Virgen de las Nieves, Granada, Spain (F.J.B.-J.). Instituto de Investigación Biosanitaria ibs Granada, Spain (F.J.B.-J.). Department of Cardiology, Complejo Hospitalario Universitario de Cáceres, Spain (M.V.M.-J.). Servicio de Cardiología del Hospital Clínico de Valladolid (HCUV), Spain (G.C.-V.). Instituto de Investigación Biosanitaria de Valladolid (IBioVALL), Spain (G.C.-V.). Heart Institute, Hospital Universitari Germans Trias i Pujol, Canyet, Badalona, Spain (A.B.-G.). Heart Failure and Inherited Cardiac Diseases Unit, Cardiology Department, Dr Balmis General University Hospital, Alicante, Spain (V.C.-P.). Institute for Health and Biomedical Research of Alicante (ISABIAL), Spain (V.C.-P.). Department of Cardiology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (IMAS12), Madrid, Spain (R.S.-B.). Facultad de Medicina, Universidad Complutense, Madrid, Spain (R.S.-B.). Cardiology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Spain (A.G.-Á.). Genética Cardiovascular, Instituto de Investigación Sanitaria de Santiago, Unidad de Cardiopatías Familiares, A Coruña, Spain (M.B.). Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain (M.B.). Cardiology, Cardiac Genetics Clinical Unit, Hospital Universitari Josep Trueta, Hospital Santa Caterina, Girona, Spain (R.B.). Cardiovascular Genetics Center and Clinical Diagnostic Laboratory, Institut d'Investigació Biomèdica Girona-IdIBGI, CIBER-CV, Salt, Spain (R.B.). Servicio de Cardiología, Unidad de Cardiopatías Familiares, Hospital Universitario y Politécnico La Fe, Spain (E.Z.). Instituto de Investigación Sanitaria La Fe, Universidad de Valencia, Spain (E.Z.). Unidad de Cardiopatías Familiares, Hospital Universitario Son Llatzer, Palma de Mallorca, Spain (T.R.-V.). Servicio de Cardiología, Unidad de Cardiopatías Familiares, Hospital Universitario Virgen del Rocío, Sevilla, Spain (M.L.P.-P.). Biostatistics Unit, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERESP, ISCIII, Madrid, Spain (A.R.). Legal Medicine and Forensic Department, Universidad de Murcia, Spain (M.S.-M.). Instituto de Investigación Sanitaria de Navarra (IdiSNA), Spain (G.L.-L., M.T.B.-E.). Universidad Francisco de Vitoria, Majadahonda, Spain (P.G.-P.).

Acknowledgments

The authors thank the research participants.

Sources of Funding

This study was funded by the Instituto de Salud Carlos III through project PI24/0359 (cofunded by the European Regional Development Fund/European Social Fund "A Way to Make Europe"/"Investing in Your Future") and by Call HORIZON-EIC-2022-PATHFINDERCHALLENGES 01 "CARDIOGENOMICS" from HORIZON European Innovation Council Grants/European Commission (DCM-NEXT project). The Centro Nacional de Investigaciones Cardiovasculares is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia, Innovación y Universidades (MICIU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (grant CEX2025-001658-S funded by MICIU AEI/10.13039/501100011033). Complejo Hospitalario Universitario Santiago de Compostela has been funded by the Instituto de Salud Carlos III through project PI22/00286. Dr Amin is supported by the EU4H-Programme of the European Union (support for the ERN GUARD-Heart project). The Amsterdam Medical Center, Hospital Universitario Puerta de Hierro, Hospital Clínic, Hospital Vall 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; <http://guardheart.ern-net.eu>).

Disclosures

None.

Supplemental Material

Methods

Tables S1–S9

Figures S1–S2

Investigators

Genetic Variants

REFERENCES

- Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet*. 2015;386:813–825. doi: 10.1016/S0140-6736(14)61282-4
- Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, Daubert JP, de Chillou C, DePasquale EC, Desai MY, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019;16:e301–e372. doi: 10.1016/j.hrthm.2019.05.007
- Schiebel K, Finsterer J, Lazarevic P, Stöllberger C. Stroke and embolism in patients with left ventricular hypertrabeculation/non-compaction. *J Stroke Cerebrovasc Dis*. 2022;31:106623. doi: 10.1016/j.jstrokecerebrovasdis.2022.106623
- Wengrofsky P, Armenia C, Oleszak F, Kupferstein E, Rednam C, Mitre CA, McFarlane SI. Left ventricular trabeculation and noncompaction cardiomyopathy: a review. *EC Clin Exp Anat*. 2019;2:267–283.
- Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J*. 2016;37:1850–1858. doi: 10.1093/eurheartj/ehv727
- Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, Kim RJ, von Knobelsdorff-Brenkenhoff F, Kramer CM, Pennell DJ, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance: 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson*. 2020;22:19. doi: 10.1186/s12968-020-00610-6
- Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol*. 2005;46:101–105. doi: 10.1016/j.jacc.2005.03.045
- Captur G, Muthurangu V, Cook C, Flett AS, Wilson R, Barison A, Sado DM, Anderson S, McKenna WJ, Mohun TJ, et al. Quantification of left ventricular trabeculae using fractal analysis. *J Cardiovasc Magn Reson*. 2013;15:36. doi: 10.1186/1532-429X-15-36
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424. doi: 10.1038/gim.2015.30
- Binder JX, Pletscher-Frankild S, Tsaou K, Stolte C, O'Donoghue SI, Schneider R, Jensen LJ. COMPARTMENTS: unification and visualization of protein subcellular localization evidence. *Database (Oxford)*. 2014;2014:bau012. doi: 10.1093/database/bau012
- Lin AY, Dinatolo E, Metra M, Sbolli M, Dasseni N, Butler J, Greenberg BH. Thromboembolism in heart failure patients in sinus rhythm: epidemiology, pathophysiology, clinical trials, and future direction. *JACC Heart Fail*. 2021;9:243–253. doi: 10.1016/j.jchf.2021.01.009
- Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, De Potter TJR, Dwight J, Guasti L, Hanke T, et al; ESC Scientific Document Group. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45:3314–3414. doi: 10.1093/eurheartj/ehae176
- Yeung C, Enriquez A, Suarez-Fuster L, Baranchuk A. Atrial fibrillation in patients with inherited cardiomyopathies. *Europace*. 2019;21:22–32. doi: 10.1093/europace/euy064
- Stöllberger C, Blazek G, Dobias C, Hanafin A, Wegner C, Finsterer J. Frequency of stroke and embolism in left ventricular hypertrabeculation/noncompaction. *Am J Cardiol*. 2011;108:1021–1023. doi: 10.1016/j.amjcard.2011.05.039
- Ritter M, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc*. 1997;72:26–31. doi: 10.4065/72.1.26
- Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol*. 2000;36:493–500. doi: 10.1016/s0735-1097(00)00755-5
- Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, Devci B, Sahin O, Kisacik HL, Korkmaz S. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail*. 2006;12:726–733. doi: 10.1016/j.cardfail.2006.08.002
- Murphy RT, Thaman R, Blanes JG, Ward D, Sevdalis E, Papra E, Kiotsekoglou A, Tome MT, Pellerin D, McKenna WJ, et al. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J*. 2005;26:187–192. doi: 10.1093/eurheartj/ehi025
- Stöllberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction. *J Am Soc Echocardiogr*. 2004;17:91–100. doi: 10.1016/S0894-7317(03)00514-5
- Stöllberger C, Wegner C, Finsterer J. CHADS₂- and CHA₂DS₂-VASc scores and embolic risk in left ventricular hypertrabeculation/noncompaction. *J Stroke Cerebrovasc Dis*. 2013;22:709–712. doi: 10.1016/j.jstrokecerebrovasdis.2011.10.014
- Greutmann M, Mah ML, Silversides CK, Klaassen S, Attenhofer Jost CH, Jenni R, Oechslin EN. Predictors of adverse outcome in adolescents and adults with isolated left ventricular noncompaction. *Am J Cardiol*. 2012;109:276–281. doi: 10.1016/j.amjcard.2011.08.043
- Amzulescu MS, Rousseau MF, Ahn SA, Boileau L, de Meester de Ravenstein C, Vancraeynest D, Pasquet A, Vanoverschelde JL, Pouleur A-C, Gerber BL. Prognostic impact of hypertrabeculation and noncompaction phenotype in dilated cardiomyopathy: a CMR study. *JACC Cardiovasc Imaging*. 2015;8:934–946. doi: 10.1016/j.jcmg.2015.04.015
- Casas G, Limeres J, Oristrell G, Gutierrez-Garcia L, Andreini D, Borregan M, Larrañaga-Moreira JM, Lopez-Sainz A, Codina-Solà M, Teixido-Tura G, et al. Clinical risk prediction in patients with left ventricular myocardial noncompaction. *J Am Coll Cardiol*. 2021;78:643–662. doi: 10.1016/j.jacc.2021.06.016
- Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, Wikstrand J, Kjekshus J, Lip GYH, Maggioni AP, et al; Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA). Risk of stroke in chronic heart failure patients without atrial fibrillation: analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials. *Circulation*. 2015;131:1486–1494. doi: 10.1161/CIRCULATIONAHA.114.013760
- Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, Pedersen L, Sørensen HT. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. *Stroke*. 2017;48:1161–1168. doi: 10.1161/STROKEAHA.116.016022
- Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakovska O, Ng KKH, Catanese L, Keltai K, Aboyans V, Alings M, et al. Stroke outcomes in the COMPASS Trial. *Circulation*. 2019;139:1134–1145. doi: 10.1161/CIRCULATIONAHA.118.035864
- Homma S, Thompson JL, Pulicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, et al; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med*. 2012;366:1859–1869. doi: 10.1056/NEJMoa1202299
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368
- Chimenti C, Lavalley C, Magnocavallo M, Alfaro M, Mariani MV, Bernardini F, Della Rocca DG, Galardo G, Severino P, Di Lullo L, et al. A proposed strategy for anticoagulation therapy in noncompaction cardiomyopathy. *ESC Heart Fail*. 2022;9:241–250. doi: 10.1002/ehf2.13694
- Ross SB, Jones K, Blanch B, Puranik R, McGeehan K, Barratt A, Semsarian C. A systematic review and meta-analysis of the prevalence of left ventricular non-compaction in adults. *Eur Heart J*. 2020;41:1428–1436. doi: 10.1093/eurheartj/ehz317
- Kawel N, Nacif M, Arai AE, Gomes AS, Hundley WG, Johnson WC, Prince MR, Stacey RB, Lima JAC, Bluemke DA. Trabeculated (non-compacted) and compact myocardium in adults: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging*. 2012;5:357–366. doi: 10.1161/CIRCIMAGING.111.971713
- Maron BJ, Towbin JA, Thiene G, Antzevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association. Contemporary definitions and classification of the cardiomyopathies: an American Heart

- Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113:1807–1816. doi: 10.1161/CIRCULATIONAHA.106.174287
33. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, et al; ESC Scientific Document Group. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–3626. doi: 10.1093/eurheartj/ehad194
 34. Caliskan K, Szili-Torok T, Theuns DA, Kardos A, Geleijnse ML, Balk AHMM, van Domburg RT, Jordaens L, Simoons ML. Indications and outcome of implantable cardioverter-defibrillators for primary and secondary prophylaxis in patients with noncompaction cardiomyopathy. *J Cardiovasc Electrophysiol*. 2011;22:898–904. doi: 10.1111/j.1540-8167.2011.02015.x
 35. Lofiego C, Biagini E, Pasquale F, Ferlito M, Rocchi G, Perugini E, Bacchi-Reggiani L, Boriani G, Leone O, Caliskan K, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. *Heart*. 2007;93:65–71. doi: 10.1136/hrt.2006.088229
 36. Stanton C, Bruce C, Connolly H, Brady P, Syed I, Hodge D, Asirvatham S, Friedman P. Isolated left ventricular noncompaction syndrome. *Am J Cardiol*. 2009;104:1135–1138. doi: 10.1016/j.amjcard.2009.05.062
 37. Stacey RB, Andersen MM, St Clair M, Hundley WG, Thohan V. Comparison of systolic and diastolic criteria for isolated LV noncompaction in CMR. *JACC Cardiovasc Imaging*. 2013;6:931–940. doi: 10.1016/j.jcmg.2013.01.014
 38. Mavrogeni S, Sfendouraki E, Theodorakis G, Kolovou G. Diagnosis, severity grading and prognosis of left ventricular non-compaction using cardiovascular magnetic resonance. *Int J Cardiol*. 2013;167:598–599. doi: 10.1016/j.ijcard.2012.09.234
 39. Escobar-Lopez L, Ochoa JP, Mirelis JG, Espinosa MA, Navarro M, Gallego-Delgado M, Barriales-Villa R, Robles-Mezcua A, Basurte-Elorz MT, Gutiérrez García-Moreno L, et al. Association of genetic variants with outcomes in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol*. 2021;78:1682–1699. doi: 10.1016/j.jacc.2021.08.039
 40. van Waning JI, Moesker J, Heijnsman D, Boersma E, Majoor-Krakauer D. Systematic review of genotype-phenotype correlations in noncompaction cardiomyopathy. *J Am Heart Assoc*. 2019;8:e012993. doi: 10.1161/JAHA.119.012993
 41. Mirelis JG, Escobar-Lopez L, Ochoa JP, Espinosa MA, Villacorta E, Navarro M, Casas G, Mora-Ayestarán N, Barriales-Villa R, Mogollón-Jiménez MV, et al. Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail*. 2022;24:1183–1196. doi: 10.1002/ehfj.2514
 42. Grigoratos C, Barison A, Ivanov A, Andreini D, Amzulescu M-S, Mazurkiewicz L, De Luca A, Grzybowski J, Masci PG, Marczak M, et al. Meta-analysis of the prognostic role of late gadolinium enhancement and global systolic impairment in left ventricular noncompaction. *JACC Cardiovasc Imaging*. 2019;12(11 Pt 1):2141–2151. doi: 10.1016/j.jcmg.2018.12.029
 43. Mora-Ayestarán N, Ochoa JP, Gómez-González C, Navarro-Peñalver M, Gallego-Delgado M, Larrañaga-Moreira JM, Robles-Mezcua A, Basurte-Elorz MT, Rodríguez-Palomares JF, Climent-Paya V, et al. Arrhythmic genotypes in dilated cardiomyopathy and risk of advanced heart failure. *Eur Heart J*. 2025;46:5222–5233. doi: 10.1093/eurheartj/ehaf605
 44. Biagini E, Ragni L, Ferlito M, Pasquale F, Lofiego C, Leone O, Rocchi G, Perugini E, Zagnoni S, Branzi A, et al. Different types of cardiomyopathy associated with isolated ventricular noncompaction. *Am J Cardiol*. 2006;98:821–824. doi: 10.1016/j.amjcard.2006.04.021
 45. Stöllberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. *Am J Cardiol*. 2002;90:899–902. doi: 10.1016/s0002-9149(02)02723-6
 46. Stähli BE, Gebhard C, Biaggi P, Klaassen S, Valsangiacomo Buechel E, Attenhofer Jost CH, Jenni R, Tanner FC, Greutmann M. Left ventricular non-compaction: prevalence in congenital heart disease. *Int J Cardiol*. 2013;167:2477–2481. doi: 10.1016/j.ijcard.2012.05.095
 47. Gati S, Chandra N, Bennett RL, Reed M, Kervio G, Panoulas VF, Ghani S, Sheikh N, Zaidi A, Wilson M, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? *Heart*. 2013;99:401–408. doi: 10.1136/heartjnl-2012-303418
 48. de la Chica JA, Gómez-Talavera S, García-Ruiz JM, García-Lunar I, Oliva B, Fernández-Alvira JM, López-Melgar B, Sánchez-González J, de la Pompa JL, Mendiguren JM, et al. Association between left ventricular noncompaction and vigorous physical activity. *J Am Coll Cardiol*. 2020;76:1723–1733. doi: 10.1016/j.jacc.2020.08.030
 49. Gati S, Papadakis M, Papamichael ND, Zaidi A, Sheikh N, Reed M, Sharma R, Thilaganathan B, Sharma S. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. *Circulation*. 2014;130:475–483. doi: 10.1161/CIRCULATIONAHA.114.008554
 50. Zemrak F, Ahlman MA, Captur G, Mohiddin SA, Kawel-Boehm N, Prince MR, Moon JC, Hundley WG, Lima JAC, Bluemke DA, et al. The relationship of left ventricular trabeculation to ventricular function and structure over a 9.5-year follow-up: the MESA study. *J Am Coll Cardiol*. 2014;64:1971–1980. doi: 10.1016/j.jacc.2014.08.035