Role of arrhythmic phenotype in prognostic stratification and management of dilated cardiomyopathy

Martina Setti[1,2†], Marco Merlo[1*†], Marta Gigli[1], Laura Munaretto[1], Alessia Paldino[1], Davide Stolfo[1,3], Carola Pio Loco[1], Kristen Medo[4], Caterina Gregorio[5,6], Antonio De Luca[1], Sharon Graw[4], Matteo Castrichini[4,7], Antonio Cannatà[1,8], Flavio Luciano Ribichini[2], Matteo Dal Ferro[1], Matthew Taylor[4], Gianfranco Sinagra[1], and Luisa Mestroni[4]

[1]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; [2]Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy; [3]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Cardiovascular Institute and Adult Medical Genetics Program, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [5]Biostatistics Unit, University of Trieste, Trieste, Italy; [6]MOX—Modeling and Scientific Computing Laboratory, Department of Mathematics, Politecnico di Milano, Milan, Italy; [7]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; and [8]Department of Cardiovascular Sciences, King's College London, London, UK

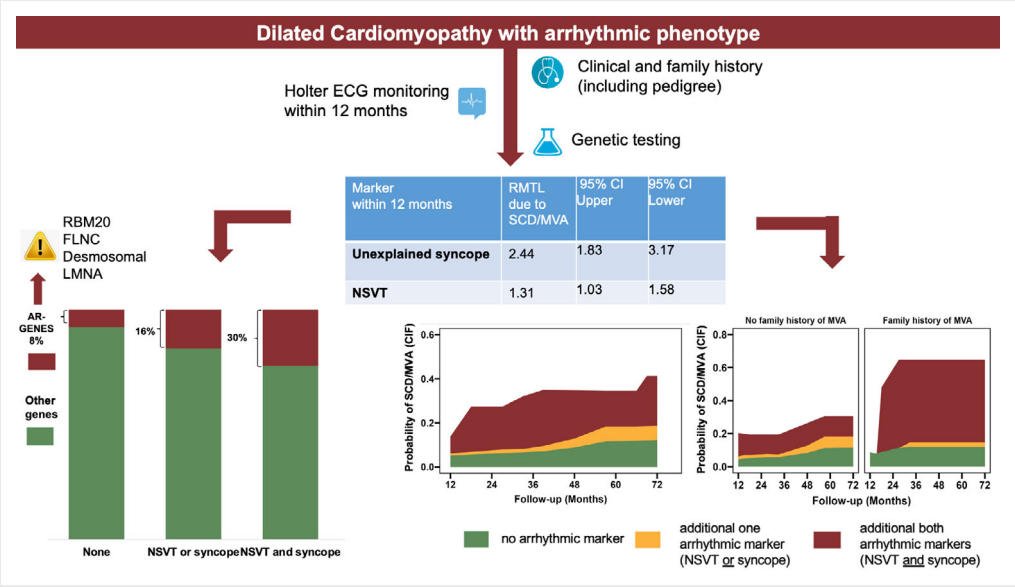
Aims Dilated cardiomyopathy (DCM) with arrhythmic phenotype combines phenotypical aspects of DCM and predisposition to ventricular arrhythmias, typical of arrhythmogenic cardiomyopathy. The definition of DCM with arrhythmic phenotype is not universally accepted, leading to uncertainty in the identification of high-risk patients. This study aimed to assess the prognostic impact of arrhythmic phenotype in risk stratification and the correlation of arrhythmic markers with high-risk arrhythmogenic gene variants in DCM patients.

Methods and results In this multicentre study, DCM patients with available genetic testing were analysed. The following arrhythmic markers, present at baseline or within 1 year of enrolment, were tested: unexplained syncope, rapid non-sustained ventricular tachycardia (NSVT), ≥1000 premature ventricular contractions/24 h or ≥50 ventricular couplets/24 h. *LMNA*, *FLNC*, *RBM20*, and desmosomal pathogenic or likely pathogenic gene variants were considered high-risk arrhythmogenic genes. The study endpoint was a composite of sudden cardiac death and major ventricular arrhythmias (SCD/MVA). We studied 742 DCM patients (45 ± 14 years, 34% female, 410 [55%] with left ventricular ejection fraction [LVEF] <35%). During a median follow-up of 6 years (interquartile range 1.6–12.1), unexplained syncope and NSVT were the only arrhythmic markers associated with SCD/MVA, and the combination of the two markers carried a significant additive risk of SCD/MVA, incremental to LVEF and New York Heart Association class. The probability of identifying an arrhythmogenic genotype rose from 8% to 30% if both early syncope and NSVT were present.

Conclusion In DCM patients, the combination of early detected NSVT and unexplained syncope increases the risk of life-threatening arrhythmic outcomes and can aid the identification of carriers of malignant arrhythmogenic genotypes.

*Corresponding author. Cardiovascular Department, Azienda Sanitaria Universitaria Integrata di Trieste and University of Trieste, Via P. Valdoni 7, 34149 Trieste, Italy. Email: marco.merlo79@gmail.com

Graphical Abstract



Dilated cardiomyopathy with arrhythmic phenotype. AR, arrhythmogenic; CI, confidence interval; CIF, cumulative incidence function; ECG, electrocardiogram; FLNC, filamin C; LMNA, lamin; MVA, major ventricular arrhythmia; NSVT, non-sustained ventricular tachycardia; RBM20, RNA binding motif 20; RMTL, restricted mean time lost; SCD, sudden cardiac death.

Keywords Dilated cardiomyopathy • Dilated cardiomyopathy with arrhythmic phenotype • Arrhythmogenic cardiomyopathy • Arrhythmogenic genotype • Non-sustained ventricular tachycardia • Unexplained syncope

Introduction

Dilated cardiomyopathy (DCM) is a primary heart muscle disease characterized by impaired contraction of left or both ventricles, representing a common cause of heart failure (HF) and one of the leading indications for heart transplantation.[1] However, its prognosis has significantly improved during the last three decades,[2] shifting the attention to the complication of sudden cardiac death (SCD) and ventricular arrhythmias as a prevention target.[3] Moreover, it has emerged that a subgroup of DCM patients can present at onset with an arrhythmic phenotype (AR-DCM).[4,5] In addition, the recent definition of arrhythmogenic cardiomyopathy has included a heterogeneous group of conditions spanning from the classic right ventricular cardiomyopathy to those predominantly involving the left ventricle (arrhythmogenic left ventricular cardiomyopathy).[6] The increasing knowledge of genotype–phenotype correlation and different clinical presentation[7] adds to the complexity of the phenotypic overlap between these entities. However, genetic testing in the real-world presents challenges of limited access, long turnaround times for results, and complex results' interpretation, thus restricting its role in the early phases of the disease, right after diagnosis. The search for feasible and reliable tools able to identify AR-DCM patients at high arrhythmic risk and with a higher probability of carrying a malignant arrhythmogenic genotype represents an unmet clinical need. Notably, in DCM, left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class are insufficient to characterize overall arrhythmogenic risk.[8–10] To address this knowledge gap, we investigated the role of specific early and easily accessible clinical and Holter electrocardiogram (ECG) arrhythmic markers in predicting adverse arrhythmic outcomes and identifying high-risk pathogenic/likely pathogenic (P/LP) variants among a large, well-clinically and genetically characterized DCM population.

Methods

Study cohort

We analysed all consecutive DCM patients with available genetic testing enrolled from 1 January 1990 to 31 December 2021 in the Familial Cardiomyopathy Registry, a multicentre (Cardiovascular Department, University of Trieste, Italy and Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, USA) ongoing project studying hereditary human cardiomyopathies, as previously described.[11] The investigation conforms with the principles outlined in the Declaration of Helsinki. All analysed patients had available genetic

testing and Holter ECG monitoring or telemetry data at baseline or within 12 months of enrolment (performed systematically in our population) other than physical examination, ECG, and echocardiogram. Time of enrolment was defined as the first evaluation at the two participating centres in the study. All patients were either initially diagnosed in the two centres or referred, and had the arrhythmic screening (Holter ECG monitoring) within 12 months of the first diagnosis. When more than one Holter ECG monitoring was performed within 12 months of enrolment, the first available was considered.

Clinical definition

The diagnosis of DCM was defined as the presence of LVEF <50%, with or without left ventricular dilatation, in the absence of any known cause of systolic impairment, including significant coronary artery disease (>50% obstruction of any major coronary artery branch) or abnormal loading conditions (history of blood pressure >160/100 mmHg, or significant organic valve disease),[12] as previously described.[2] Alcohol intake >80–100 g/day for over 10 years, previous cardiotoxic chemotherapy, an advanced systemic disease affecting short-term prognosis, congenital heart diseases, persistent supraventricular tachyarrhythmias, and active myocarditis were considered exclusion criteria.[13] Finally, patients fulfilling the phenotypic criteria for arrhythmogenic right ventricular cardiomyopathy, according to the 2010 Task Force diagnostic criteria,[14] were excluded from the study, as previously reported.[11] In all patients, family history was extensively investigated, and three-generation pedigrees were constructed when data were available.[15] A family history of major ventricular arrhythmias (MVA) was considered present if at least one family member (up to third-degree) had a major arrhythmic event (see 'Endpoint' section for definition) at <60 years.[8]

On the basis of previous reports,[4] the following were considered as markers of early arrhythmic phenotype: (i) unexplained syncope, likely due to ventricular tachyarrhythmias according to clinical judgment; (ii) rapid non-sustained ventricular tachycardia (NSVT), defined as ≥5 consecutive ventricular beats, lasting <30 s, with a rate ≥120/min on 24 h Holter monitoring or telemetry; (iii) ≥1000 premature ventricular contractions (PVCs) in 24 h; and (iv) ≥50 ventricular couplets

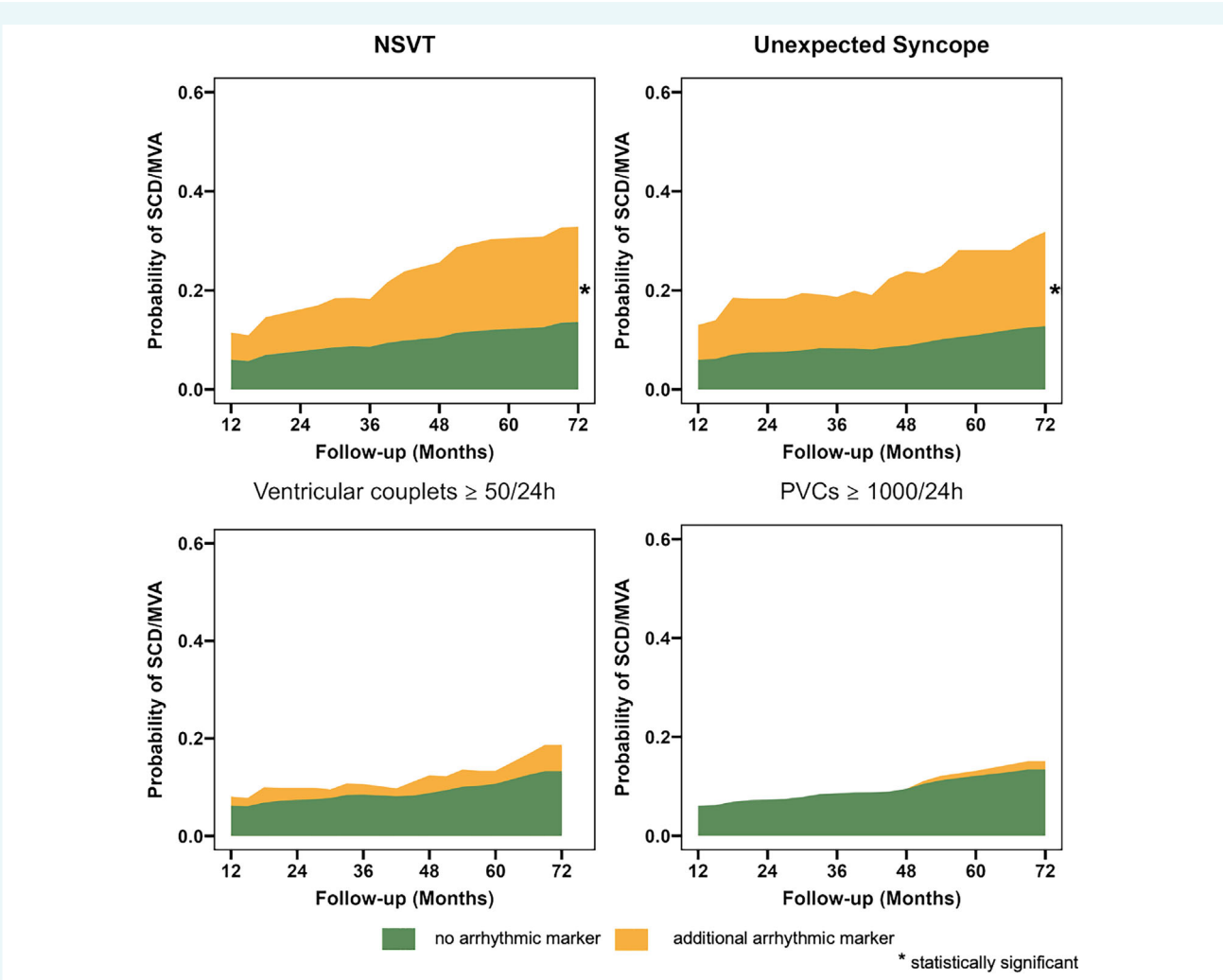


Figure 1 Probability of sudden cardiac death/major ventricular arrhythmias (SCD/MVA), according to the occurrence of non-sustained ventricular tachycardia (NSVT), unexplained syncope, ventricular couplets ≥50/24 h, and ventricular premature ventricular contractions (PVCs) ≥1000/24 h within the first year of enrolment.

in 24 h, all occurred before or after 12 months from enrolment. Arrhythmia could be documented at Holter ECG monitoring or telemetry.

Genetic test analysis

Genetic testing was performed by next-generation DNA sequencing, as previously reported.[11] Gene variants were classified as P/LP according to the American College of Medical Genetics and Genomics criteria (ACMG).[16] Only carriers (probands and affected relatives) of P/LP variants in genes with robust disease associations[17,18] were considered to be 'genotype positive' for the purposes of this study. Inside the cohort of P/LP carriers, patients were separately grouped by gene or 'functional' cluster, as previously described.[7,11] *LMNA*, *FLNC*, *RBM20*, and desmosomal gene (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*) variants were considered the high-risk arrhythmogenic genes.[7]

Endpoint

The study endpoint was a composite of SCD or MVA (SCD/MVA). Specifically, SCD was defined as witnessed SCD with or without documented ventricular fibrillation or death within 10 h of acute symptoms, or nocturnal death with no antecedent history of immediate worsening symptoms. MVA were defined as resuscitated cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia and appropriate implantable cardiac defibrillator (ICD) interventions (appropriate ICD shocks and anti-tachycardia pacing therapies). The outcome status of the patients was obtained through an extensive evaluation of informatics and paper information sources. Patients were censored at the time of their first endpoint event or the last evaluation. Events occurring from the time of enrolment were included.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables were expressed as percentages. Group comparisons were performed using analysis of variance with appropriate post hoc multiple comparisons. Probabilities of SCD/MVA, taking into account the possible competing risks of death different from SCD, were estimated using Markov Cox multi-state models. Specifically, the probability of SCD/MVA, conditioned on the fact that subjects could either have developed an arrhythmic marker in the first 12 months or not, was estimated and compared by means of the ratio of restricted mean time lost (RMTL) due to SCD/MVA.[19,20] The RMLT corresponds to the area under the cumulative incidence function up to a time horizon of 6 years (i.e. median follow-up time), and it is an intuitive way to summarize and compare cumulative incidence functions across groups without requiring the assumption of proportional hazards.[20] Confidence intervals (CI) were obtained using 100 non-parametric bootstrap repetitions. Patients with MVA at the diagnosis were excluded from the statistical analysis regarding the risk of SCD/MVA. Finally, to quantify the incremental prognostic information given by the detection of early arrhythmic markers, we assessed a comparison between the areas under the curve (AUCs) obtained through the time-dependent receiver operating characteristic (ROC) curve of the multi-state model considering only clinically reliable baseline covariates (age, sex, NYHA class, LVEF) to the one obtained also incorporating early arrhythmic markers (NSVT and unexplained syncope).

As an internal validation, to obtain the ROC curves the dataset was divided into 'train' and 'test' according to the study centre. Specifically, the centre with the largest sample size was chosen as 'train' (Italian centre), the other as 'test' (US centre). The models were estimated on the 'train' dataset and then the discrimination of the models was assessed through the ROC curve using the 'test' dataset.

Table 1 Baseline characteristics of the overall population according to clinical arrhythmic markers

	Overall population (*n* = 742)	No arrhythmic markers (*n* = 467)	Single arrhythmic marker (NSVT or syncope) (*n* = 248)	Both arrhythmic markers (NSVT and syncope) (*n* = 27)	*p*-value
Age, years	45 ± 14	44 ± 14	47 ± 13	45 ± 11	0.01
Female sex, *n* (%)	250 (34)	167 (36)	72 (29)	11 (40)	0.1
Caucasian ethnicity, *n* (%)	684 (92)	429 (92)	228 (92)	27 (100)	0.4
Family history of MVA, *n* (%)	121 (16)	82 (18)	32 (13)	7 (26)	0.1
NYHA class II–IV, *n* (%)	453 (61)	260 (58)	177 (76)	16 (67)	<0.0001
LBBB, *n* (%)	161 (22)	104 (22)	54 (22)	3 (11)	0.4
LVEF <35%, *n* (%)	410 (55)	225 (49)	168 (68)	17 (63)	<0.0001
LVEF, *n* (%)	33 ± 11	34 ± 11	29 ± 11	31 ± 11	<0.0001
LVEDD, mm	63 ± 10	62 ± 9	66 ± 10	65 ± 10	<0.0001
ACEi/ARB/ARNi, *n* (%)	621 (84)	375 (81)	223 (91)	23 (85)	0.002
Beta-blockers, *n* (%)	650 (88)	397 (86)	227 (92)	26 (96)	0.01
MRA, *n* (%)	295 (40)	191 (41)	94 (38)	10 (37)	0.5
ICD at baseline, *n* (%)	66 (9)	33 (7)	31 (12)	2 (7)	0.06
ICD implantation during follow-up, *n* (%)	287 (39)	138 (30)	131 (53)	18 (67)	<0.0001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MRA, mineralocorticoid receptor antagonist; MVA, major ventricular arrhythmia; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association.

Statistical analyses were performed using packages R version 4.1.3 (packages 'survival', 'mstate', 'ggplot2', 'timeROC'). A p-value <0.05 was considered statistically significant.

Results

Study cohort and genetics

Of the 781 patients potentially eligible, nine genotype-positive patients without criteria for DCM (i.e. LVEF >50%) and 30 patients with missing information on Holter ECG or telemetry monitoring data within 12 months of enrolment were excluded. Finally, a cohort of 742 DCM patients were enrolled, 195 (26%) from the Cardiovascular Department of Denver and 547 (74%) from the Cardiovascular Department of Trieste (online supplementary *Figure* S1). Mean age was 45 ± 14 years, 250 (34%) were female, and 410 (55%) patients had LVEF <35%. A total of 289 disease-related variants (39%) were identified from 671 families, while the remaining 453 patients tested negative (n = 233, 31%) or classified as variants of uncertain significance (n = 220, 30%). The majority of carriers (121 out of 289, 42%) showed a titin gene truncating variant, and 88 (30%) showed an arrhythmogenic genotype (39 *LMNA*, 31 *FLNC*, 1 *PKP2*, 13 *DSP*, 4 *RBM20*). The remaining gene clusters included 16 (6%) structural cytoskeleton Z-disk gene carriers, 47 (16%) sarcomeric gene carriers, and 17 (6%) with 'other genes', 7 of them variants of *SCN5A*.

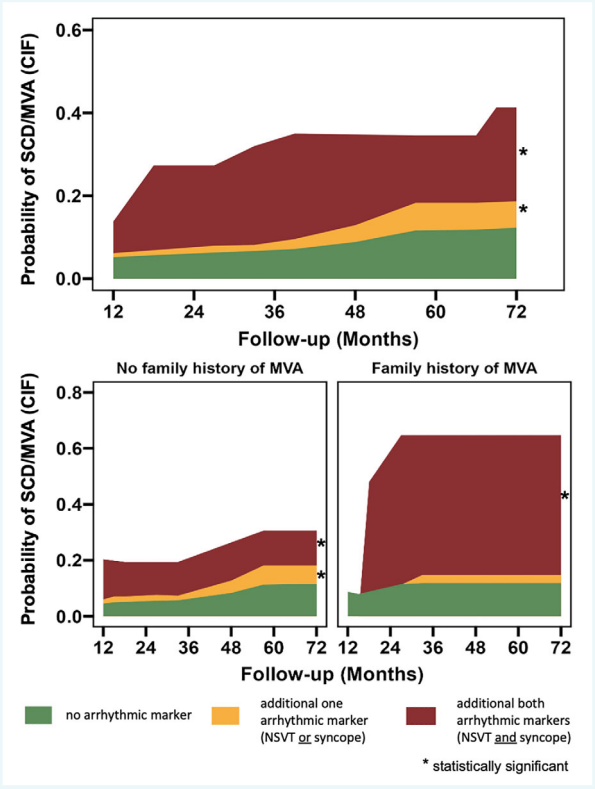


Figure 2 Probability of sudden cardiac death/major ventricular arrhythmias (SCD/MVA), based on the occurrence of early arrhythmic markers (non-sustained ventricular tachycardia [NSVT] and/or unexplained syncope—upper panel) and the family history of MVA (bottom panel). Curves show the graded risk of SCD/MVA, also considering when family history of MVA is or is not present: group 0 (none arrhythmic markers, neither early syncope nor NSVT—green curve), group 1 (one arrhythmic marker, early syncope or NSVT—yellow curve), group 2 (two arrhythmic markers, both early syncope and NSVT—red curve). CIF, cumulative incidence function.

Prognostic relevance of early arrhythmic markers

Over a median follow-up of 6 years (interquartile range 1.6–12.1), 180 (24%) patients experienced the study endpoint (15 [2%] SCD, and 165 [22%] MVA). The mean probability of SCD/MVA was 22% (95% CI 18–26%) at 10 years.

A total of 226 (31%) patients had NSVT, 76 (10%) unexplained syncope, 103 (14%) > ventricular couplets/24 h, and 260 (35%) >1000 PVCs/24 h at baseline evaluation or within the first year of enrolment. In the time-to-event analysis, patients with unexplained syncope had a RMTL due to the endpoint 2.44 times higher than patients without unexplained syncope (RMTL ratio: 2.44 [1.83–3.17]), and patients with NSVT 1.31 times higher than patients without early NSVT (RMTL ratio: 1.31 [1.03–1.58]) (*Figure 1*, online supplementary *Table S1*). No other early arrhythmic markers emerged as associated with the study endpoint. A total of 467 out of 742 patients (63%) did not show unexplained syncope or NSVT, 248 (33%) had a single arrhythmic marker (i.e. unexplained syncope [n = 49] or NSVT [n = 199]) and 27 (4%) presented both arrhythmic markers (i.e. unexplained syncope and NSVT) (*Table 1*). Interestingly, patients with at least one arrhythmic marker had worse baseline LVEF and higher left ventricular size. The prevalence of family history of MVA was similar between groups (p = 0.1).

The probability of SCD/MVA at 6 years progressively increased from 12% in patients without early unexplained syncope nor NSVT to 35% in patients with both arrhythmic markers. The excess in risk was prominent within the first 2 years of follow-up and then persisted during the long term (*Figure 2*, upper panel). Of note, the coexistence of a positive family history of MVA significantly increased the strength of the association of early syncope and NSVT with the risk of SCD/MVA (*Figure 2*, bottom panel, *Graphical Abstract*).

When early NSVT and unexplained syncope were added to a model considering only age, sex, NYHA class and LVEF, an increase in AUC from 0.75 to 0.86 (95% CI for the increase in the AUC of the second model: 0.002–0.39) was obtained.

At sensitivity analyses, the probability of SCD/MVA in patients with early syncope and NSVT was confirmed to be higher in both subgroups of patients presenting with or without a family history of MVA (online supplementary *Table S2A*, *Figure S2A,B*). Furthermore, unexplained syncope and NSVT were confirmed to increase the probability of SCD/MVA only in the male population (online supplementary *Table S2B*, *Figure S2C,D*). Finally, a total of 308

patients (42%) had an available cardiac magnetic resonance (CMR). NSVT and unexplained syncope were confirmed as predictors of SCD/MVA in the CMR subgroup (RMTL ratio: 1.89 [1.33–2.54]) and in patients with late gadolinium enhancement on CMR (RMTL ratio: 1.85 [1.24–2.89]).

The models were internally validated in the US sub-cohort ('test'), after fitting them onto the Italian centre ('train').

Arrhythmogenic genotypes

In our cohort, the rate of arrhythmogenic genotypes significantly increased from 8% in DCM patients without arrhythmic markers to 16% in those with at least one between early syncope and NSVT, up to 30% in DCM patients with both (*Figure 3*, *Graphical Abstract*). In the small percentage of patients with two arrhythmic markers and a family history of MVA ($n = 7$, 1%), the rate of arrhythmogenic genotypes rose up to 57%. Results were consistent when each centre was considered separately (online supplementary *Figure S3*).

The role of evaluating early NSVT, unexplained syncope and family history of MVA in the identification of high-risk DCM patients carrying an arrhythmogenic genotype (i.e. *LMNA*, *FLNC*, *RBM20*, and desmosomal genes) is presented in *Figure 4*.

Discussion

Main findings

The lack of survival benefit from primary prevention ICD implantation in non-ischaemic systolic HF patients, shown in the DANISH trial,[21] raises the need for improving the arrhythmic stratification of patients with DCM. Despite the impact of arrhythmic stratification recently provided by genetic testing and CMR,[3] the availability of early, accessible, and reproducible markers of arrhythmic risk, useful for a first-line risk assessment, remains an unmet clinical need. In the present study, in a large clinically and genetically well-characterized DCM cohort, followed for 6 years, we (i) identified two arrhythmic markers, NSVT and unexplained syncope, holding value for SCD/MVA prediction when assessed at baseline or within the first year of enrolment, particularly when a family history of MVA coexisted; and (ii) demonstrated that the same markers are also highly prevalent in carriers of arrhythmogenic genotypes (i.e. *LMNA*, *FLNC*, *RBM20*, and desmosomal genes). Those findings hold relevant clinical impact in managing the early phases of DCM and re-addressing arrhythmic stratification to specific high-risk patients: in patients with early NSVT and syncope, regardless of the LVEF and NYHA class, lower thresholds for genetic testing and other second- or third-line arrhythmic risk stratification (i.e. CMR, loop recorder) might be promptly proposed.

Our results highlight the overlap between arrhythmogenic cardiomyopathy and DCM, definitely leading to a paradigm shift in DCM: from a disease mainly characterized by HF to a more complex condition, where both HF and arrhythmias may dominate the clinical picture in a continuum of disease. Indeed, early NSVT and/or syncope were associated with higher left ventricular size and lower LVEF at enrolment (*Table 1*). Interestingly, the time of detecting arrhythmic markers is pivotal: they should be promptly

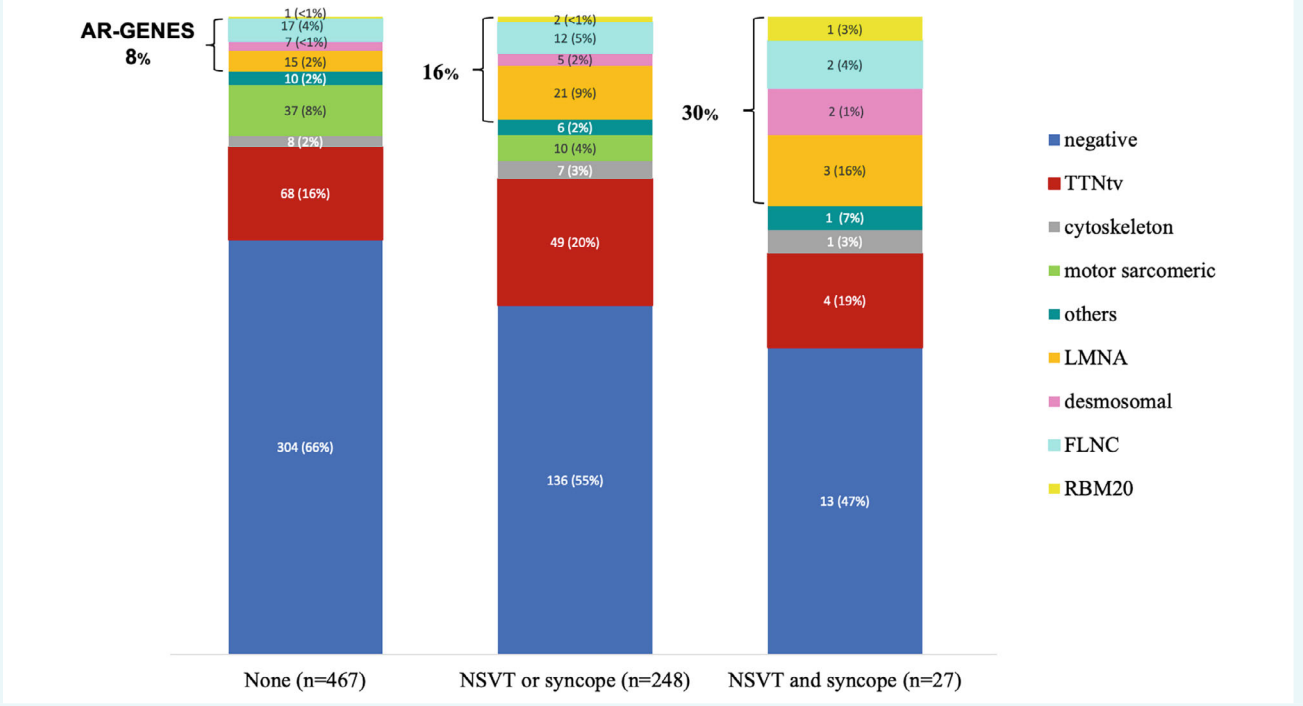


Figure 3 Efficacy of arrhythmic markers in identifying arrhythmogenic (AR) genotypes. FLNC, filamin C; LMNA, lamin; NSVT, non-sustained ventricular tachycardia; RBM20, RNA binding motif 20; TTNtv, titin-truncating variant; cytoskeleton, structural cytoskeleton Z-disk variant.

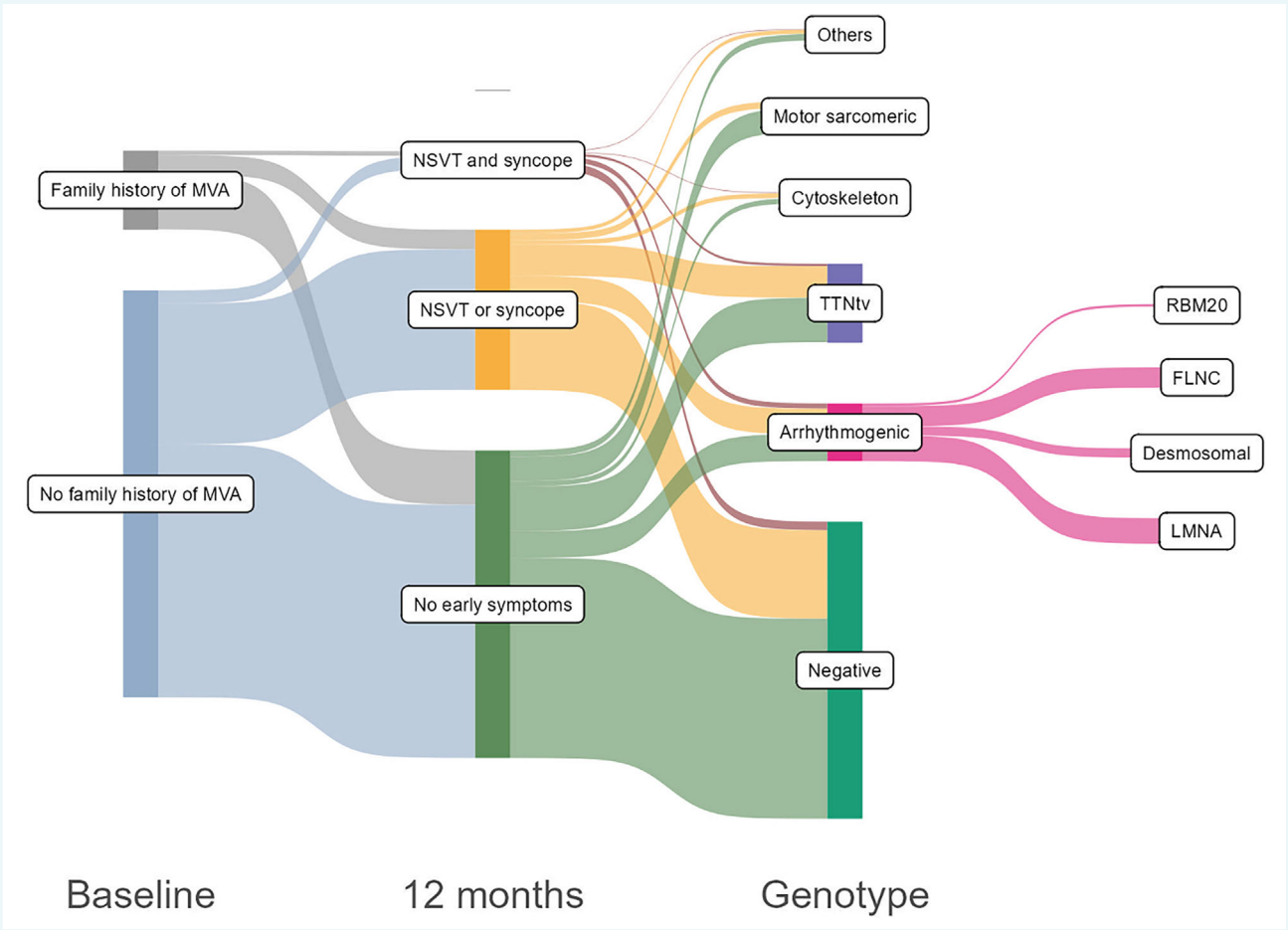


Figure 4 Visual representation of the role of early arrhythmic phenotype (non-sustained ventricular tachycardia [NSVT] and unexplained syncope within the first year of enrolment) and family history of major ventricular arrhythmias (MVA) in identifying arrhythmogenic genotypes. The width of the flows and height of the nodes are directly proportional to the number of patients they represent. FLNC, filamin C; LMNA, lamin; RBM20, RNA binding motif 20; TTNtv, titin-truncating variant; cytoskeleton, structural cytoskeleton Z-disk variant.

searched during the initial phases of the disease, in order to further address the deeper assessment of the risk of SCD.

The impact of non-sustained ventricular tachycardia and unexplained syncope

By examining each arrhythmic marker, frequent PVCs (≥1000/24 h) and ventricular couplets (≥50/24 h) were not associated with SCD/MVA also in previous series. The prognostic role of PVCs and ventricular couplets is still unclear, and conflicting data have been previously published.[22] Indeed, it may be challenging to establish whether PVCs are the direct consequence of left ventricular systolic dysfunction (PVC-induced cardiomyopathy),[23] an arrhythmic manifestation in patients with structural cardiomyopathy, or an innocent by-stander. The presence of frequent PCVs and couplets should not generally dictate alone the choice of ICD in primary prevention. However, not only the burden but also a better characterization of PVCs, particularly their morphology and axis (i.e. right bundle branch block superior axis)[24] and when associated with corresponding myocardial fibrosis at CMR, may help in identifying patients who should be considered for ICD implantation. On the contrary, NSVT and unexplained syncope in the first phases of the disease were demonstrated to be accurate in identifying the highest-risk patients with AR-DCM, incremental to age, sex, and conventional markers of arrhythmic risk (i.e. LVEF and NYHA class), with an additive value of the combination of the two markers.[25,26] Remarkably, early unexplained syncope has been recognized as a risk factor for SCD/MVA also for other cardiomyopathies, such as arrhythmogenic right ventricular cardiomyopathy[14] and hypertrophic cardiomyopathy,[27] confirming the importance of an accurate clinical evaluation. The lack of SCD/MVA stratification in women agreed with previous findings,[28] highlighting how the arrhythmic profile in women is more challenging to define. The reasons beyond this sex-related difference in the results are currently unknown and deserve more attention in future studies. However, a role of sex hormones has been postulated, besides the fact that it may reflect a less prevalent and thus less represented female population. Finally, in this study, we

have endorsed the additive role of the family history of MVA to arrhythmic phenotype in the risk stratification of DCM patients for SCD/MVA. A systematic, early and careful clinical history, including a family history of at least three generations, as recommended by current guidelines,[3,12] is a crucial step not only for diagnostic purposes but also for the further management of DCM patients.

Arrhythmogenic genotype

Another key finding of the present study is that early detection of NSVT and unexplained syncope was associated with a higher prevalence (i.e. 30%) of arrhythmogenic genotypes, namely *LMNA*, *FLNC*, *RBM20*, and desmosomal genes. According to the recent guidelines,[3,12,29] recognition of some malignant genotypes is essential because it may lead to different therapeutic approaches (specifically early primary prevention ICD implantation in patients with LVEF >35%). Again, those arrhythmic markers were useful tools in order to address genetic testing in familial and sporadic forms of DCM. Emerging data suggest that other genes (e.g. titin-truncating variants) are prone to MVA also in the early phase of the disease[30]; future multicentre studies are needed to consolidate knowledge on other arrhythmogenic genotypes and better refine their prognostic implication.

Study limitations

This study has some limitations. First, although based on patients prospectively enrolled in our registry, it carries the intrinsic limits of retrospective studies. Second, the enrolment has been conducted in two tertiary referral centres for cardiomyopathy, leading to a potential selection and referral bias. Third, a threshold of 120 bpm for NSVT (instead of 150 bpm, as previous used[4]) was chosen before analysing the data, to harmonize the study with current clinical practice in the participating centres and to improve sensibility of the marker at the expense of specificity. Future studies focused on the identification of the most effective threshold of NSVT are needed. Furthermore, during the prolonged follow-up of the study, HF therapy has considerably improved; therefore, there might be interactions between the time of the first evaluation and the endpoint. Finally, P/LP variants in *PLN* gene could be underestimated because they have not been systematically tested in the DCM cohort since 2019. Although an internal validation confirmed the results, to generalize the present data, the findings need to be confirmed in a large external multicentre cohort comprehensively studied. Classification of cardiomyopathies is constantly evolving, as shown by the recent European Society of Cardiology guidelines,[12] which have included the new concept of non-dilated left ventricular cardiomyopathy, not specifically analysed in this study. This category deserves future studies for assessing its epidemiology, outcomes, and therapeutic management.

Conclusions

The presence of single or both arrhythmic phenotypes, namely NSVT and unexplained syncope within 1 year of enrolment, can significantly improve the arrhythmic prognostic stratification of DCM patients and increase the likelihood of malignant arrhythmogenic genotypes, mostly in the presence of a family history of MVA. Consequently, a comprehensive clinical evaluation by systematic Holter ECG monitoring and family data might represent a useful, easily-accessible, first-line strategy for the initial arrhythmic risk assessment in DCM patients when genetics and CMR are not systematically available.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, *et al.* 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. https://doi.org/10.1161/CIRCULATIONAHA.106.174287
2. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, *et al.* Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1111–1121. https://doi.org/10.1002/ejhf.1914
3. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. https://doi.org/10.1093/eurheartj/ehac262
4. Spezzacatene A, Sinagra G, Merlo M, Barbati G, Graw SL, Brun F, *et al.*; Familial Cardiomyopathy Registry. Arrhythmogenic phenotype in dilated cardiomyopathy: Natural history and predictors of life-threatening arrhythmias. *J Am Heart Assoc* 2015;**4**:e002149. https://doi.org/10.1161/JAHA.115.002149
5. Zegkos T, Panagiotidis T, Parcharidou D, Efthimiadis G. Emerging concepts in arrhythmogenic dilated cardiomyopathy. *Heart Fail Rev* 2021;**26**:1219–1229. https://doi.org/10.1007/s10741-020-09933-z
6. Lukas Laws J, Lancaster MC, Ben Shoemaker M, Stevenson WG, Hung RR, Wells Q, *et al.* Arrhythmias as presentation of genetic cardiomyopathy. *Circ Res* 2022;**130**:1698–1722. https://doi.org/10.1161/CIRCRESAHA.122.319835
7. Paldino A, Dal Ferro M, Stolfo D, Gandin I, Medo K, Graw S, *et al.* Prognostic prediction of genotype vs phenotype in genetic cardiomyopathies. *J Am Coll Cardiol* 2022;**80**:1981–1994. https://doi.org/10.1016/j.jacc.2022.08.804
8. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, *et al.* Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers a European cohort study. *J Am Coll Cardiol* 2012;**59**:493–500. https://doi.org/10.1016/j.jacc.2011.08.078
9. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, *et al.* Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol* 2016;**68**:2440–2451. https://doi.org/10.1016/j.jacc.2016.09.927
10. De Angelis G, Merlo M, Barbati G, Bertolo S, De Luca A, Ramani F, *et al.* Longitudinal arrhythmic risk assessment based on ejection fraction in patients with recent-onset nonischemic dilated cardiomyopathy. *J Am Soc Echocardiogr* 2022;**35**:801–809.e803. https://doi.org/10.1016/j.echo.2022.03.019
11. Gigli M, Merlo M, Graw SL, Barbati G, Rowland TJ, Slavov DB, *et al.* Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2019;**74**:1480–1490. https://doi.org/10.1016/j.jacc.2019.06.072
12. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.*; ESC Scientific Document Group. ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**2023**:3503–3626. https://doi.org/10.1093/eurheartj/ehad194
13. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, *et al.* Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: Changing mortality over the last 30 years. *Eur J Heart Fail* 2014;**16**:317–324. https://doi.org/10.1002/ejhf.16

14. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the task force criteria. *Circulation* 2010;**121**:1533–1541. https://doi.org/10.1161/CIRCULATIONAHA.108.840827
15. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, *et al.* Genetic evaluation of cardiomyopathy – a Heart Failure Society of America practice guideline. *J Card Fail* 2018;**24**:281–302. https://doi.org/10.1016/j.cardfail.2018.03.004
16. Richards S, Aziz N, Bale S, Bick D, das S, Gastier-Foster J, *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. https://doi.org/10.1038/gim.2015.30
17. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, *et al.* International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. *Circ Genom Precis Med* 2021;**14**:e003273. https://doi.org/10.1161/CIRCGEN.120.003273
18. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, *et al.* Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation* 2021;**144**:7–19. https://doi.org/10.1161/CIRCULATIONAHA.120.053033
19. Lyu J, Hou Y, Chen Z. The use of restricted mean time lost under competing risks data. *BMC Med Res Methodol* 2020;**20**:197. https://doi.org/10.1186/s12874-020-01040-9
20. Perego C, Sbolli M, Specchia C, Fiuzat M, McCaw ZR, Metra M, *et al.* Utility of restricted mean survival time analysis for heart failure clinical trial evaluation and interpretation. *JACC Heart Fail* 2020;**8**:973–983. https://doi.org/10.1016/j.jchf.2020.07.005
21. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, *et al.*; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230. https://doi.org/10.1056/NEJMoa1608029
22. Ataklte F, Erqou S, Laukkanen J, Kaptoge S. Meta-analysis of ventricular premature complexes and their relation to cardiac mortality in general populations. *Am J Cardiol* 2013;**112**:1263–1270. https://doi.org/10.1016/j.amjcard.2013.05.065
23. Chugh SS, Shen WK, Luria DM, Smith HC. First evidence of premature ventricular complex-induced cardiomyopathy: A potentially reversible cause of heart failure. *J Cardiovasc Electrophysiol* 2000;**11**:328–329. https://doi.org/10.1111/j.1540-8167.2000.tb01802.x
24. Muser D, Nucifora G, Pieroni M, Castro SA, Casado Arroyo R, Maeda S, *et al.* Prognostic value of nonischemic ringlike left ventricular scar in patients with apparently idiopathic nonsustained ventricular arrhythmias. *Circulation* 2021;**143**:1359–1373. https://doi.org/10.1161/CIRCULATIONAHA.120.047640
25. Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and nonischemic dilated cardiomyopathy: Prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985;**55**:146–151. https://doi.org/10.1016/0002-9149(85)90317-0
26. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, *et al.* Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA investigators. *Circulation* 1996;**94**:3198–3203. https://doi.org/10.1161/01.cir.94.12.3198
27. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, *et al.* Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* 2009;**119**:1703–1710. https://doi.org/10.1161/CIRCULATIONAHA.108.798314
28. Cannatà A, Fabris E, Merlo M, Artico J, Gentile P, Pio Loco C, *et al.* Sex differences in the long-term prognosis of dilated cardiomyopathy. *Can J Cardiol* 2020;**36**:37–44. https://doi.org/10.1016/j.cjca.2019.05.031
29. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
30. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Sabater Molina M, *et al.* Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the. *Circ Heart Fail* 2020;**13**:e006832. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006832