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**CLINICAL RESEARCH**
*Heart failure and cardiomyopathies*

# Clinical features and outcomes in carriers of pathogenic desmoplakin variants

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**See the editorial comment for this article 'Desmoplakin cardiomyopathy: a step towards understanding the genetic basis of phenotypic and outcome heterogeneity', by A. Tsatsopoulou *et al*., https://doi.org/10.1093/eurheartj/ehae714.**


## Abstract

**Background and Aims** Pathogenic variants in the desmoplakin (*DSP*) gene are associated with the development of a distinct arrhythmogenic cardiomyopathy phenotype not fully captured by either dilated cardiomyopathy (DCM), non-dilated left ventricular cardiomyopathy (NDLVC), or arrhythmogenic right ventricular cardiomyopathy (ARVC). Prior studies have described baseline *DSP* cardiomyopathy genetic, inflammatory, and structural characteristics. However, cohort sizes have limited full clinical characterization and identification of clinical and demographic predictors of sustained ventricular arrhythmias (VAs), heart failure (HF) hospitalizations, and transplant/death. In particular, the relevance of acute myocarditis-like episodes for subsequent disease course is largely unknown.

**Methods** All patients with pathogenic/likely pathogenic (P/LP) *DSP* variants in the worldwide *DSP*-ERADOS Network (26 academic institutions across nine countries) were included. The primary outcomes were the development of sustained VA and HF hospitalizations during follow-up. Fine–Gray regressions were used to test association between clinical and instrumental parameters and the development of outcomes.

**Results** Eight hundred patients [40.3 ± 17.5 years, 47.5% probands, left ventricular ejection fraction (LVEF) 49.5 ± 13.9%] were included. Over 3.7 [1.4–7.1] years, 139 (17.4%, 3.9%/year) and 72 (9.0%, 1.8%/year) patients experienced sustained VA and HF episodes, respectively. A total of 32.5% of individuals did not fulfil diagnostic criteria for ARVC, DCM, or NDLVC; their VA incidence was 0.5%/year. In multivariable regression, risk features associated with the development of VA were female sex [adjusted hazard ratio (aHR) 1.547; $P = .025$], prior non-sustained ventricular tachycardia (aHR 1.721; $P = .009$), prior sustained VA (aHR 1.923; $P = .006$), and LVEF ≤ 50% (aHR: 1.645; $P = .032$), while for HF, they were the presence of T-wave inversion in 3+ electrocardiogram leads (aHR 2.036, $P = .007$) and LVEF ≤ 50% (aHR 3.879; $P < .001$). Additionally, 70 (8.8%) patients experienced a myocardial injury episode at presentation or during follow-up. These episodes were associated with an increased risk of VA and HF thereafter (HR 2.394; $P < .001$, and HR 5.064, $P < .001$, respectively).

**Conclusions** Patients with P/LP *DSP* variants experience high rates of sustained VA and HF hospitalizations. These patients demonstrate a distinct clinical phenotype (*DSP* cardiomyopathy), whose most prominent risk features associated with adverse clinical outcomes are the presence of prior non-sustained ventricular tachycardia or sustained VA, T-wave inversion in 3+ leads on electrocardiogram, LVEF ≤ 50%, and myocardial injury events.


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## Structured Graphical Abstract


### Key Question

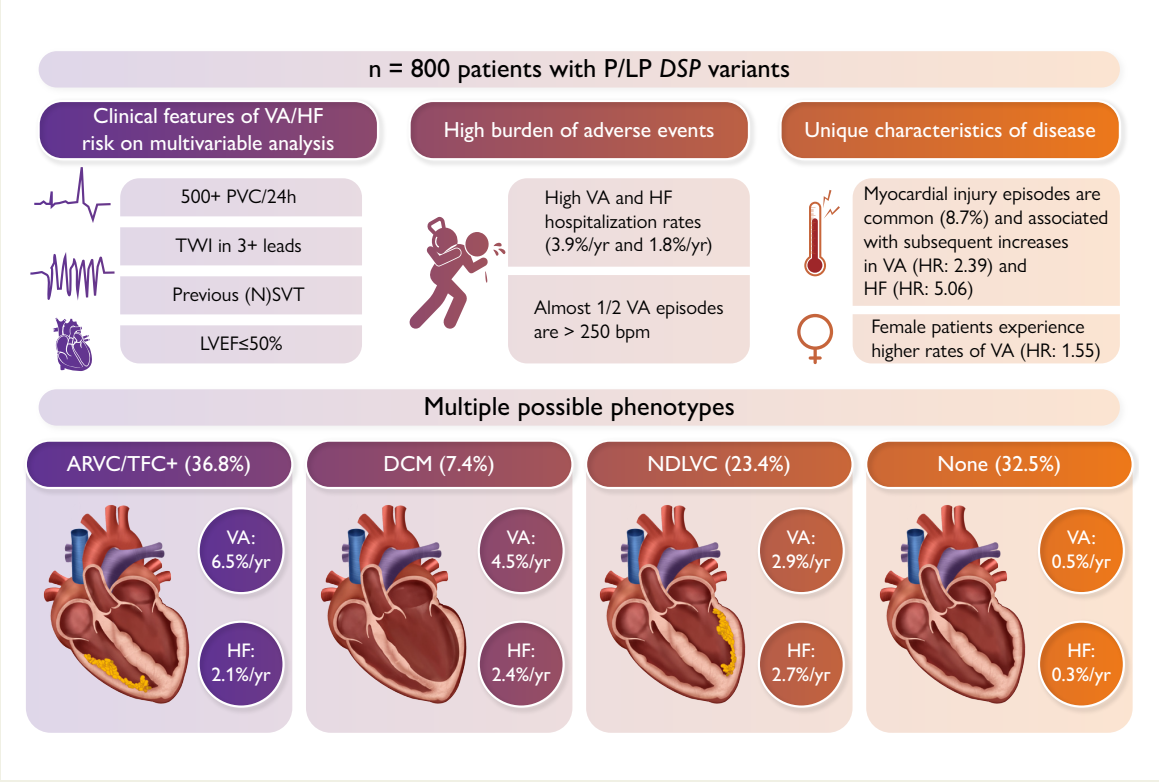
Clinical characteristics and predictors of ventricular arrhythmias (VA) and heart failure (HF) hospitalizations in patients harboring pathogenic/likely-pathogenic (P/LP) desmoplakin (DSP) gene variants have been poorly described. In particular, the relevance of myocarditis-like episodes for subsequent disease course is largely unknown.

### Key Finding

In 800 patients with P/LP DSP variants, the prevalence of VA or HF episodes was 3.9%/y and 1.8%/y respectively during a 3.7-year follow-up period. The most prominent risk features were prior non-sustained or sustained VA, T-wave inversion in three or more leads on ECG, left ventricular ejection fraction ≤50% and myocarditis episodes.

### Take Home Message

Patients harboring P/LP DSP demonstrate a distinct clinical phenotype, ECG derangement, frequent ventricular ectopy, and a high VA/HF risk. Inflammatory myocardial injury is common and causes an increase in patient risk for VA and HF hospitalization.


Graphical summary reporting the main findings of the study. Features associated with risk of events include predictors from multivariable models as well as analysis of implications of myocardial injury episodes. aHR, adjusted hazard ratio; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; (N)SVT, (non)sustained ventricular tachycardia; PVC, premature ventricular contraction; TFC, 2010 Task Force Criteria; TWI, T-wave inversion; VA, ventricular arrhythmia. Created with BioRender.com.

**Keywords** DSP • Desmoplakin • DSP cardiomyopathy • Hot phases • ACM

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# Introduction

Historically, clinical strategies for the management of arrhythmogenic cardiomyopathies have been based on phenotype and clinical diagnosis,[1,2] rather than patients' underlying genetic substrates. This 'phenotype-first' approach is fundamental to modern cardiology and is the basis for inclusion and exclusion criteria of innumerable clinical studies. As a result, the phenotypic characterization of patients is inextricably linked to our current understanding of the risk factors, clinical outcomes, and therapeutic options of these diseases.

Thanks to the expanding availability of genetic testing, this phenotype-first paradigm has begun to shift.[3–5] Recent reports have demonstrated the prognostic superiority of genotype-based classification for management of familial arrhythmogenic and dilated cardiomyopathies, and gene-specific arrhythmic risk stratification algorithms have been proposed.[5–10]

The cardiomyopathy associated with pathogenic and likely pathogenic (P/LP) variants in desmoplakin (*DSP*) is a clinical spectrum likely to benefit from a gene-specific approach. Desmoplakin is a cardiac desmosomal protein that plays a critical role in myocardial force transmission.[11] Historically P/LP *DSP* variants have been associated with both arrhythmogenic right ventricular cardiomyopathy (ARVC)[12,13] and dilated cardiomyopathy (DCM) phenotypes with a high ventricular arrhythmia (VA) burden.[3,14,15] Several *DSP*-specific features, including recurrent myocarditis-like episodes and a unique pattern of left ventricular (LV) fibrosis on imaging, also seem to differentiate this clinical entity from both ARVC and DCM.[16–19] While these findings suggest that *DSP*-related cardiomyopathy may represent a distinct, gene-associated class of cardiomyopathy, previous studies of *DSP*-variant carriers have been largely underpowered for the identification of clinical risk factors associated with arrhythmia and heart failure (HF) outcomes. Here, we present the largest international, gene-specific cohort of patients harbouring P/LP *DSP* variants. Leveraging the collaborative effort of 26 centres worldwide, we describe the clinical characteristics and natural history of *DSP*-related cardiomyopathy with a focus on factors associated with development of sustained VA and HF including the significance of the myocarditis-like episodes for clinical course.

# Methods

## Study population

The study population was drawn from the *DSP*-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) network, an international collaboration including 26 academic institutions (Johns Hopkins University, Boston Children's Hospital, Montreal Heart Institute, University Hospital of Trieste, University of Colorado Anschutz Medical Campus, Policlinico Casilino Hospital, Garvan Institute of Medical Research, University Hospital of Zurich, Fondazione Cardiocentro Ticino Lugano, Royal Melbourne Hospital, University Hospital of Florence, University College of London, University Hospital of Amsterdam, University Hospital of Groningen, University Hospital of Utrecht, University Hospital of Bologna, IRCCS Centro Cardiologico Monzino, Brigham and Women's Hospital, Hôpital Universitaire Pitié-Salpêtrière, University of Michigan Medical Center, Imperial College London, Geisinger Health System, Muenster University Hospital, Stanford University Hospital, San Raffael Hospital, Ospedali Riuniti University Hospital Ancona) across nine countries (USA, Canada, Italy, Australia, Switzerland, UK, The Netherlands, France, and Germany).

Patients followed at any of the HF, arrhythmia, cardiomyopathy, sudden cardiac death (SCD), family screening, or transplant clinics/registries of each institution in the *DSP*-ERADOS network were screened for potential inclusion in the study. Patients were included in the study if they met the following criteria: (i) harboured a P/LP variant in *DSP*[20]; (ii) were alive at the time of the first assessment; and (iii) clinical follow-up was available after first assessment at the enrolling institution.

The study conforms to the Helsinki Declaration and was performed in accordance with regulations set forth by local institutional review/ethics boards. Data supporting this manuscript are available upon reasonable request to the corresponding author.

## Data collection strategy

Historical data were collected independently at each institution according to a set of standardized definitions. Available demographics, patient medical history, genetic test results, and baseline cardiac instrumental exams [12-lead electrocardiogram (ECG), echocardiography, cardiac magnetic resonance (CMR), 24 h Holter ECG monitoring] were retrieved for each patient, if available. Number of leads with T-wave inversion (TWI) was calculated excluding lead aVR. Outcomes were adjudicated locally at each centre via review of ECG, implantable cardioverter-defibrillator (ICD) interrogations, and patient medical records. All *DSP* genetic variants categorized as P or LP locally underwent centralized expert review by specialists in cardiac genetics (B.M., C.A.J.), in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines and previously published ACM specific ACMG adjustments.[20,21] The Supplementary Material Section—Genetics lists the variants of all study participants. Nonsense-mediated decay (NMD) regions in the *DSP* gene were defined and grouped as per a previous study on the topic.[22] In brief, truncating and splice variants were classified by the predicted potential for a variant at that transcript (cDNA) location to trigger NMD. Regions fall in one of three categories (as per the description by Hoorntje *et al.*[22]) (i) constitutive and NMD competent (at the N-terminal; exons 1–22, part of exon 23, c.1-c.3582); (ii) non-constitutive and NMD competent (in the central rod domain; *DSPI*/*DSPIa* c.3583-c.4050 and *DSPI* c.4051-c.5379); and (iii) a constitutive but NMD-incompetent region (at the C-terminus; exon 24; c.5324-8616).

Probands were defined as the first affected individual in a family who came to medical attention. Primary prevention patients were defined as patients without any of the VA or HF study outcomes at first assessment, while those presenting with a historical event were defined as secondary prevention. Secondary prevention patients were further stratified into VA secondary prevention or HF secondary prevention depending on the nature of the historical event prior to first assessment. The ARVC phenotype was defined in accordance to the 2010 Task Force Criteria (TFC). Dilated cardiomyopathy phenotype for patients harbouring P/LP *DSP* variants was defined as LV ejection fraction (LVEF) $\leq$ 50% and presence of LV dilation after careful exclusion of secondary causative aetiologies and in the absence of a definite ARVC diagnosis in accordance to the previous literature.[2,5,23] Non-dilated LV cardiomyopathy (NDLVC) was defined in accordance to the recent European Society of Cardiology (ESC) guidelines as an LVEF $\leq$ 50% and/or presence of LV late gadolinium enhancement (LGE) in the absence of both LV dilation and definite ARVC diagnosis[24]; these patients were further stratified by the presence or absence of systolic dysfunction (LVEF $\leq$ 50%). Phenotype-negative individuals were defined by the absence of any of the above *DSP*-related disease phenotypes based on available clinical testing; patients without CMR were assumed to be negative for LGE. This was a complete-case analysis, and missing test results were not imputed. Episodes of myocardial injury were defined as a symptomatic cardiac chest pain of non-coronary artery disease origin (after exclusion with a coronary artery computed tomography and/or catheterization) with an increase in serum cardiac troponin levels above the 99th percentile.

## Study outcomes

The primary outcomes were the development of (i) sustained VA during patient follow-up, defined as a composite of the occurrence of sustained ventricular tachycardia (VT) (lasting $\geq$30 s at $\geq$100 b.p.m. or with haemodynamic compromise requiring cardioversion), appropriate ICD interventions, ventricular fibrillation/flutter (VF), and sudden cardiac arrest (SCA)/SCD episodes, and (ii) HF hospitalizations. Secondary outcomes included the development of (i) rapid sustained VA episodes (defined as a combination of sustained VT, appropriate ICD interventions on events with a cycle rate > 250 b.p.m. and >30 s, VF, or SCA/SCD), and (ii) a composite of LV assist device (LVAD) implantation, heart transplantation (HTx), and overall mortality (LVAD/HTx/death).

## Statistical analysis

Analyses were performed using STATA v.14.0 (StataCorpLLC, 4905 Lakeway Drive, College Station, TX, USA) and Python version 3.9.13 using the open-source Pandas (v.2.0.2), SciPy (v1.11.0), and Statsmodels (v.0.14.0) statistical code libraries. The normality of distribution of all continuous variables was tested using a Shapiro–Wilk test for normality. Normally distributed variables were reported as mean (±standard deviation), while non-normally distributed variables were reported as median [interquartile range (IQR)]. Categorical variables were reported as count (%). Comparisons between continuous variables were performed using independent Student's *t*-test or a Wilcoxon rank sum test, as appropriate. Categorical variables were compared using $\chi^2$ or

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Fisher exact test, as appropriate. For time-dependent survival analyses, follow-up duration was calculated from the date of first evaluation (baseline) to the date of reaching the specific endpoint or censoring, which was defined as death from any cause, HTx, or the last available clinical follow-up. The probability of survival free from the outcome of interest was estimated using the Kaplan–Meier method.

After graphically checking for the proportionality of hazards, the association between baseline predictors and outcomes of interest were tested using a Fine–Gray regression considering overall mortality as a competing event. Subhazard ratios (HRs) were reported. For the composite outcome of LVAD/HTx/death, no competing events were possible and therefore a Cox regression was used and HR reported. Multivariable Fine–Gray or Cox regression models, including only predictors derived from baseline clinical characteristics and cardiac instrumental evaluations available in >85% of the patient cohort (ECG and echocardiography) and with a univariable *P*-value of <.10, were then fitted. An additional set of multivariable models was built using baseline characteristics and data from either 24 h Holter ECGs or CMR in the sub-cohorts for which those data were available ($n = 546$ and $n = 506$, respectively), and reported in the Supplementary Material. Strength of association of predictors included in the Fine–Gray or Cox regression models was quantified using (adjusted) (sub)hazard ratios. To test for familial clustering, all the final models were also run as multilevel survival models using the variables included in the final multivariate model as fixed effects and family clustering as a random effect. No significant changes were observed in final results. To test for associations between the occurrence of myocardial injury during follow-up and the occurrence of subsequent outcomes of interest (e.g. sustained VA or HF hospitalizations), time-varying Cox regression analyses were performed, with a history of myocardial injury as a time-dependent covariate. To assess the relative risk of the event of interest that was associated with myocardial injury, HR are reported, and event-free survival curves for patients with and without a history of myocardial injury are presented. A *P*-value of ≤.05 was considered statistically significant.

# Results

## Defining clinical features of DSP cardiomyopathy

Of the 800 patients harbouring a single heterozygous *DSP* P/LP variant enrolled in our cohort, the mean age was 40.3 ± 17.5 years, 504 (63.0%) were women, and 380 (47.5%) were probands. Most patients ($n = 659$; 82.4%) had a *DSP* truncating variant, while 65 (8.1%) had a splice variant, and 76 (9.5%) had a missense variant. Patients had been followed for 3.7 [1.4–7.1] years at enrolment. Most patients were actively being followed by their local centre, with date of last clinical follow-up within the preceding 36 months in all but 33 of living patients without LVAD or transplant.

The most common reasons for initial evaluation of enrolled patients were family screening ($n = 320$; 40.0%), arrhythmias ($n = 138$; 17.3%), and non-arrhythmic symptoms of probable *DSP*-specific origin, including chest pain and shortness of breath ($n = 254$; 31.8%). Palpitations and dyspnoea at the time of the initial clinical evaluation were reported in 253 (31.6%) and 277 (34.6%) patients, respectively. Sustained VA episodes, HF hospitalizations, and syncopal episodes at or prior to initial assessment were experienced by 100 (12.5%), 80 (10.0%), and 87 (10.9%) patients, respectively. A total of 164 (20.5%) patients were qualified as secondary prevention ($n = 84$ VA secondary prevention; $n = 64$ HF secondary prevention, with an additional $n = 16$ qualifying for both subgroups). From a diagnostic perspective, 294 (36.8%) patients fulfilled a definite diagnosis for ARVC in accordance with the 2010 TFC, 59 (7.4%) patients fulfilled the criteria for DCM, and 187 (23.4%) fulfilled a NDLVC phenotype, including 100 (12.5%) with normal systolic function but presence of LV LGE. *Table 1* summarizes the baseline characteristics of the patient cohort. Supplementary data online, *Table S1* stratifies baseline characteristics by proband status. Supplementary data online, *Table S2* stratifies baseline characteristics by primary vs. secondary prevention status. Supplementary data online, *Table S3* reports baseline characteristics of patients with no VA events at first presentation and an ICD. Supplementary data online, *Table S4A* reports the characteristics of individuals ($n = 260$, 32.5%) not fulfilling any of the three phenotypes at baseline. Supplementary data online, *Table S5* reports characteristics of patients/individuals fulfilling different cardiomyopathic phenotypes at baseline.

Baseline 12-lead ECG assessment was available for 97.8% ($n = 782$) of the cohort. T-wave inversion was not uncommon, with 67 (8.6%) patients presenting with TWI in leads V1–V3, 63 (8.1%) with TWI in ≥2 inferior leads, and 109 (13.9%) with TWI spanning V4–V6. Besides V1, the most common locations of TWI were V5 and V6 (17.8% each).

LV function assessment was available for most patients at initial evaluation ($n = 760$, 95.0%). Mean LVEF was mildly reduced (49.5 ± 13.9%) on average, with 320 (42.1%) and 133 (17.5%) patients presenting LVEF ≤ 50% and ≤35%, respectively. *Table 2* and Supplementary data online, *Tables S6 and S7* report detailed data on cardiac instrumental assessments available at baseline, including echocardiography ($n = 709$, 88.6%; LVEF 49.6 ± 14.6%), 24 h Holter ECG ($n = 534$, 66.8%; median 24 h premature ventricular contraction [PVC] burden 600 [17–2529]; 53.4% > 500 PVC/24 h), and CMR imaging ($n = 551$, 68.9%; right ventricular ejection fraction [RVEF] 51.6 ± 10.6%; LVEF 50.7 ± 12.4; presence of LGE $n = 361/551$, 65.5%). Overall, 489 (61.1%) patients had all tests available at baseline, with 534 (66.8%) patients having ECG, Holter, and plus one imaging exam.

## Patient outcomes

Over a median follow-up of 3.7 [1.4–7.1] years, 139 patients (17.4%; 3.9% [3.3–4.6]/year incidence rate) experienced a sustained VA, with 69 (8.6% of patients; 1.8% [1.4–2.2]/year incidence rate) experiencing a rapid sustained VA episode. Those patients without previous sustained VA at the time of initial evaluation experienced a lower but still substantial incidence rate of sustained VA episodes during follow-up (14.6%; 3.2% [2.6–3.9]/year incidence rate). Heart failure hospitalization was experienced by 72 patients (9.0%; 1.8% [1.4–2.3]/year incidence rate). At the last available follow-up, 38 (4.8%) patients had undergone a heart transplant, 4 (0.5%) had an LVAD placed, and 30 (3.8%) patients had died. *Table 3* summarizes the study outcomes for the entire patient cohort. Supplementary data online, *Figure S1* reports Kaplan–Meier curves for each outcome in the full cohort. Supplementary data online, *Table S8* reports outcomes by primary vs. secondary prevention status, which are displayed graphically in Supplementary data online, *Figure S2*.

Patients with a diagnosis of definite ARVC, DCM, or NDLVC experienced high rates of sustained VAs and HF hospitalizations in follow-up (ARVC: 6.5% [5.4–7.9]/year overall VA rate; 2.1% [1.5–2.9]/year HF hospitalization rate; DCM: 4.5% [2.5–8.1]/year overall VA rate; 2.4% [1.1–5.3]/year HF hospitalization rate; NDLVC: 2.9% [2.0–4.5]/year overall VA rate; 2.7% [1.8–4.1]/year HF hospitalization rate). Event rates for NDLVC patients with LGE on CMR and an LVEF > 50% ($n = 100$) were as follows: 1.9% [0.9–4.1]/year overall VA rate; 0.5% [0.1–2.1]/year HF hospitalization rate. Event rate for NDLVC patients with LVEF ≤ 50% instead was as follows: 3.6% [2.3–5.9]/year overall VA rate, 4.4 [2.9–6.9]/year HF hospitalization rate. Supplementary data online, *Figure S3* displays freedom from VA and HF episodes in individuals with NDLVC who had presence of LGE but normal systolic function compared to those with systolic dysfunction. Individuals with NDLVC and preserved LV function (LVEF > 50%) with LGE experienced lower rates of

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**Table 1 Cohort characteristics**

| | Overall (*n* = 800) | Female (*n* = 504) | Male (*n* = 296) | *P* |
|---|---|---|---|---|
| Age at baseline, mean ± SD | 40.3 ± 17.5 | 40.8 ± 17.6 | 39.3 ± 17.4 | .237 |
| Probands, *n* (%) | 380 (47.5) | 245 (48.6) | 135 (45.6) | .412 |
| Ethnicity | | | | |
| White, *n* (%) | 740 (92.5) | 464 (92.1) | 276 (93.2) | .540 |
| Hispanic, *n* (%) | 19 (2.4) | 12 (2.4) | 7 (2.4) | .989 |
| African-American/Black, *n* (%) | 14 (1.8) | 10 (1.9) | 4 (1.4) | .510 |
| South Asian, *n* (%) | 21 (2.6) | 15 (3.0) | 6 (2.0) | .418 |
| East Asian, *n* (%) | 6 (0.8) | 3 (0.6) | 3 (1.0) | 0.508 |
| Reason for presentation | | | | |
| Arrhythmic presentation, *n* (%) | 138 (17.3) | 84 (16.7) | 54 (18.2) | .569 |
| Non-arrhythmic presentation, *n* (%) | 254 (31.8) | 163 (32.3) | 91 (30.7) | .639 |
| Family screening, *n* (%) | 320 (40.0) | 191 (37.9) | 129 (43.6) | .113 |
| Incidental findings, *n* (%) | 88 (11.0) | 66 (13.1) | 22 (7.4) | **.013** |
| Palpitations at baseline, *n* (%) | 253 (31.6) | 189 (37.5) | 64 (21.6) | **<.001** |
| Dyspnoea at baseline, *n* (%) | 277 (34.6) | 178 (35.3) | 99 (33.5) | .591 |
| NYHA I, *n* (%) | 125 (45.1) | 72 (40.5) | 53 (53.5) | **.036** |
| NYHA II, *n* (%) | 101 (36.5) | 70 (39.3) | 31 (31.3) | .184 |
| NYHA III/IV, *n* (%) | 51 (18.4) | 36 (20.2) | 15 (15.1) | .297 |
| *DSP* variant type | | | | |
| Truncation, *n* (%) | 659 (82.4) | 421 (83.5) | 238 (80.4) | .263 |
| Splice site, *n* (%) | 65 (8.1) | 41 (8.1) | 24 (8.1) | .989 |
| Missense, *n* (%) | 76 (9.5) | 42 (8.3) | 34 (11.5) | .142 |
| Variant region (*n* = 722/461/261 non-missense) | | | | |
| Constitutive NMD competent, *n* (%) | 403 (55.8) | 260 (56.4) | 143 (54.8) | .676 |
| Non-constitutive NMD competent, *n* (%) | 138 (19.1) | 97 (21.0) | 41 (15.7) | .080 |
| Constitutive NMD incompetent, *n* (%) | 181 (25.1) | 104 (22.6) | 77 (29.5) | **.039** |
| Dermatological features, *n* (%) | 182 (22.8) | 118 (23.4) | 64 (21.6) | .560 |
| History of NSVT at baseline, *n* (%) | 164 (20.5) | 118 (23.4) | 46 (15.5) | **.008** |
| History of HF, *n* (%) | 80 (10.0) | 56 (11.1) | 24 (8.1) | .172 |
| History of syncope, *n* (%) | 87 (10.9) | 57 (11.3) | 30 (10.1) | .606 |
| Sustained VA at/prior to presentation, *n* (%) | 100 (12.5) | 55 (10.9) | 45 (15.2) | .076 |
| Diagnostic criteria fulfilment | | | | |
| ARVC, *n* (%) | 294 (36.8) | 196 (38.9) | 98 (33.1) | .102 |
| DCM, *n* (%) | 59 (7.4) | 37 (7.3) | 22 (7.4) | .962 |
| NDLVC, *n* (%) | 187 (23.4) | 107 (21.2) | 80 (27.0) | .062 |
| Therapy at baseline | | | | |
| BB, *n* (%) | 380 (47.5) | 254 (50.4) | 126 (42.6) | **.032** |
| AAD, *n* (%) | 86 (10.8) | 54 (10.7) | 32 (10.8) | .966 |

*Continued*

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**Table 1 Continued**

| | Overall (*n* = 800) | Female (*n* = 504) | Male (*n* = 296) | *P* |
|---|---|---|---|---|
| Ace/ARB, *n* (%) | 280 (35.0) | 180 (35.7) | 100 (33.8) | .580 |
| MRA, *n* (%) | 89 (11.2) | 66 (13.2) | 23 (7.8) | **.020** |
| ICD at baseline (within 3 months), *n* (%) | 151 (18.9) | 98 (19.4) | 53 (17.9) | .591 |

*P* values < 0.05 have been bolded.
AAD, anti-arrhythmic drug; ARB, angiotensin receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; BB, beta-blocker; DCM, dilated cardiomyopathy; *DSP*, desmoplakin; HF, heart failure; NDLVC, non-dilated left ventricular cardiomyopathy; MRA, mineralocorticoid receptor antagonist; NMD, nonsense-mediated decay; NYHA, New York Heart Association; NSVT, non-sustained ventricular tachycardia; VA, ventricular arrhythmia.

HF hospitalizations than those with systolic dysfunction (LVEF ≤ 50%) (log-rank *P* < .001); while there was a trend towards lower rates of sustained VA in patients with NDLVC and preserved LV function with LGE, this difference did not reach statistical significance (*P* = .076).

Interestingly, the VA rate experienced by individuals not fulfilling any phenotype by diagnostic criteria was low (0.5% [0.2–1.2]/year overall VA; 0.3% [0.1–0.9]/year fast VA), as was the rate of HF hospitalization (0.3% [0.1–0.9]/year) (*Figure 1*). Individuals not fulfilling typical diagnostic categories of *DSP*-related disease phenotype (e.g. ARVC, DCM, or NDLVC) who experienced VA and/or HF episodes during follow-up had a higher PVC burden and a lower LVEF on initial evaluation (see Supplementary data online, *Table S4A*). Specific clinical characteristics of the seven individuals experiencing a *DSP*-related adverse outcome are presented on a case-by-case basis in Supplementary data online, *Table S4B*.

## Outcome predictors

*Table 4* reports the complete univariable Fine–Gray and Cox regression models for the primary and secondary outcomes. Notably, risk factors were similar across outcomes. History of previous non-sustained ventricular tachycardia (NSVT) or prior sustained VA was strongly associated with future arrhythmic events, as they were associated with a higher risk of sustained VA (HR 2.692 [1.909–3.798], *P* < .001; HR 2.568 [1.764–3.737], *P* < .001, respectively). Non-sustained ventricular tachycardia was also associated with HF hospitalization during follow-up (HR 1.491 [1.026–2.741], *P* = .042). Prior sustained VA was also associated with both secondary outcomes (HR 3.415 [2.043–5.711], *P* < .001 for LVAD/HTx/Death; HR 3.676 [2.239–6.038], *P* < .001 for fast VA). Among the electrophysiologic parameters tested, the presence of TWI on 12-lead ECG and a higher PVC burden at a 24 h Holter ECG were also associated with higher rates of both VA and HF hospitalizations. Premature ventricular contraction burden on Holter was likewise associated with fast VA. Similarly, evidence of LV and RV systolic dysfunction was strongly associated with an increased risk of all primary and secondary outcomes. LVEF measured on either echocardiogram or CMR predicted VA and HF hospitalizations. Right ventricular ejection fraction as estimated on CMR and presence of moderate to severe RV dysfunction on echocardiogram were also associated with increased incidence of sustained VA.

Finally, the fulfilment of a cardiomyopathy phenotype was associated with an increased risk of both primary outcomes in a Fine–Gray model, with an ARVC phenotype more strongly associated with the occurrence of sustained VA events (ARVC phenotype: HR 13.946 [5.678–34.253], *P* < .001; NLVCM: HR 6.228 [2.405–16.125], *P* < .001; DCM phenotype: HR 9.247 [3.242–26.373], *P* < .001) and the NDLVC and DCM phenotypes with HF hospitalizations (NDLVC HR 9.560 [2.858–31.982; *P* < .001]; DCM phenotype: HR 9.173 [2.270–37.058], *P* = .002; ARVC phenotype: HR 7.849 [2.399–25.686], *P* = .001). Supplementary data online, *Figure S4* graphically reports variations of the HR of association with sustained VA depending on the threshold used for different variables (most significant threshold: combined LVEF%: ≤ 50%; PVC burden: PVC > 500; leads with TWI: 3+ TWI).

Multivariable Fine–Gray models for any sustained VA and HF occurrence in patients for whom ECG and echocardiography data were available (*n* = 709) were fitted and reported in *Table 5* (all patients) and Supplementary data online, *Table S9* (patients with loss of function variants only). For VA, a history of previous non-sustained or sustained VA, female sex, and LVEF ≤ 50% were all independent markers of increased risk. When including only those patients with loss of function variants, predicted susceptibility to NMD was likewise an independent marker of VA risk (see Supplementary data online, *Table S9*). When considering HF hospitalizations as well as the combined LVAD/HTx/death outcome, reduced LVEF was the strongest independent risk factor. Finally, Supplementary data online, *Tables S10* and *S11* report the multivariable Fine–Gray models including Holter and CMR characteristics.

## Myocardial injury events

Myocardial injury events were relatively common, with 70 patients experiencing at least one (8.8%; *n* = 20 at presentation; *n* = 50 during follow-up). Twenty-one (2.6%) patients had multiple (≥2) distinct episodes. Supplementary data online, *Table S12* reports baseline characteristics of these patients. As shown in *Figure 2*, these episodes portended a worse clinical course. The occurrence of a myocardial injury episode was associated with an increased risk of sustained VA (HR 2.394 [1.498–3.827], *P* < .001) and of HF hospitalization (HR 5.064 [2.847–9.004], *P* < .001) thereafter. For patients experiencing a sustained VA after the myocardial injury event (*n* = 18), the median time between myocardial injury and VA was 0.7 [0.5–4.6] years.

## Sex differences

Women were highly represented in our study cohort, both overall (*n* = 504, 63.0%) and among probands (probands: 245/380, 64.5% female; family members: 259/420, 61.7% female). As shown in *Table 1*, while female patients had more symptomatic palpitations on initial evaluation (37.5% female vs. 21.6% male, *P* < .001) and a higher prevalence of NSVT (23.4% female vs. 15.5% male; *P* = .008) clinical presentation of male and female patients was otherwise similar. Upon cardiac evaluation, however, female patients demonstrated more evidence of electrophysiological derangement, including more TWI on baseline ECG (0 [1–3] female vs. 0 [1–2] male, *P* = .007) and higher burdens of PVC (731 [18–2769] female vs. 400 [12–1538] male, *P* = .026)

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**Table 2 Instrumental characteristics of the study cohort**

| | |
|---|---|
| **ECG at baseline (n = 782)** | |
| ECG data available, *n* (%) | 782 (97.8) |
| PR interval (ms), median [IQR] | 160 [140–173] |
| QRS interval (ms), median [IQR] | 92 [84–103] |
| N of TWI on 12-lead ECGs, median [IQR] | 1 [0–3] |
| TWI in ≥3 precordial leads, ***n*** (%) | 199 (24.9) |
| TWI V1–V3, *n* (%) | 67 (8.6) |
| TWI in ≥2 inferior leads, *n* (%) | 63 (8.1) |
| TWI V4–V6, *n* (%) | 109 (13.9) |
| TAD, *n* (%) | 81 (10.4) |
| **Echocardiogram at baseline (n = 709)** | |
| Echocardiogram data available, *n* (%) | 709 (88.6) |
| RV assessment (*n* = 703) | |
| Normal function, *n* (%) | 602 (85.6) |
| Mild reduction, *n* (%) | 57 (8.1) |
| Moderate reduction, *n* (%) | 25 (3.6) |
| Severe reduction, *n* (%) | 19 (2.7) |
| RVWMA, *n* (%) | 48 (6.8) |
| LV assessment (*n* = 709) | |
| LVEF, mean ± SD | 49.6 ± 14.6 |
| LVWMA, *n* (%) | 160 (22.6) |
| **Holter at baseline (n = 534)** | |
| Holter data available, *n* (%) | 534 (66.8) |
| PVC burden, median [IQR] | 600 [17–2529] |
| PVC > 500/24 h, *n* (%) | 285 (53.4) |
| PVC > 1000/24 h, *n* (%) | 226 (42.3) |
| **CMR at baseline (n = 551)** | |
| CMR data available, *n* (%) | 551 (68.9) |
| RVEDVi, median [IQR] | 80.0 [69.0–100.0] |
| RVEF (%), mean ± SD | 51.6 ± 10.6 |
| RVWMA, *n* (%) | 92 (16.7) |
| LVEDVi, median [IQR] | 87.1 [73.4–106.5] |
| LVEF (%), mean ± SD | 50.7 ± 12.4 |
| LVWMA, *n* (%) | 138 (25.0) |
| LGE, *n* (%) | 361 (65.5) |
| Septum LGE, *n* (%) | 190 (34.5) |
| LV LGE, *n* (%) | 292 (53.0) |

ECG, electrocardiogram; LGE, late gadolinium enhancement; LV, left ventricular; LVWMA, left ventricular wall motion abnormality; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; RV, right ventricular; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVWMA, right ventricular wall motion abnormality; TAD, terminal activation delay; TWI, T-wave inversion.

**Table 3 Follow-up data**

| **Follow-up (years), median [IQR]** | **3.7 [1.4–7.1]** |
|---|---|
| Patient with sustained VA, *n* (%) | 139 (17.4) |
| Fast VA, *n* (%) | 69 (8.6) |
| HF hospitalizations, *n* (%) | 72 (9.0) |
| LVAD placement, *n* (%) | 4 (0.5) |
| Transplant, *n* (%) | 38 (4.8) |
| Death, *n* (%) | 30 (3.8) |

HF, heart failure; IQR, interquartile range; LVAD, left ventricular assist device; VA, ventricular arrhythmia.

(see Supplementary data online, *Tables S6* and *S7*). In contrast, right ventricular function was modestly lower in males (mean RVEF 53.0 ± 9.5 female vs. 49.2 ± 11.8 male, $P < .001$). No sex differences in DCM, NDLVC, or ARVC fulfilment were observed (7.3% vs. 7.4% DCM, $P = .962$; 21.2% vs. 27.0% NDLVC, $P = .062$; 38.9% vs. 33.1% ARVC, $P = .102$). Supplementary data online, *Figure S5* reports survival curves for sustained VA and HF hospitalizations by sex. Female sex was associated with increased sustained VA in both univariable ($P = .047$) and multivariable analyses ($P = .025$) (*Table 5*). Sex was not associated with HF hospitalization, LVAD/CT/death, or fast VA.

# Discussion

To this day, the clinical course of patients harbouring P/LP variants in the *DSP* gene (*DSP* cardiomyopathy), and particularly the risk factors associated with worse outcomes, has not been fully described, in part due to the relatively small size of available study cohorts. In this study, we characterized the disease-specific clinical features and long-term risk profiles of 800 patients harbouring P/LP *DSP* variants ascertained from 26 academic institutions in nine countries (*DSP*-ERADOS Network). The main findings include (*Structured Graphical Abstract*):

(1) Over a median of 3.7 years of follow-up, patients harbouring a P/LP DSP variant had a high risk of sustained VA, fast VA, HF hospitalizations, and LVAD/HTx/death in follow-up (17.4%, 8.6%, 9.0%, and 8.3% of the cohort, respectively; 3.9%/year, 1.8%/year, 1.8%/year, and 1.6%/year incidence rates).
(2) The arrhythmic risk of patients harbouring DSP variants with no history of sustained VAs at baseline was similarly high (14.6%; 3.2%/year incidence rate) which is particularly notable given the inclusion of at-risk variant carriers in the cohort.
(3) Diagnostic criteria for ARVC, NDLVC, and DCM were fulfilled in 36.8%, 23.4%, and 7.4% of patients with DSP P/LP variants, respectively. Around a third of the cohort did not meet criteria for any cardiomyopathy phenotype at baseline. These individuals were at relatively low risk for sustained VA (0.5%/year overall VA rate; 0.3%/year fast VA rate).
(4) Unlike in other arrhythmogenic cardiomyopathies, females with P/LP DSP variants had a higher risk for sustained VA events than males (aHR 1.548).

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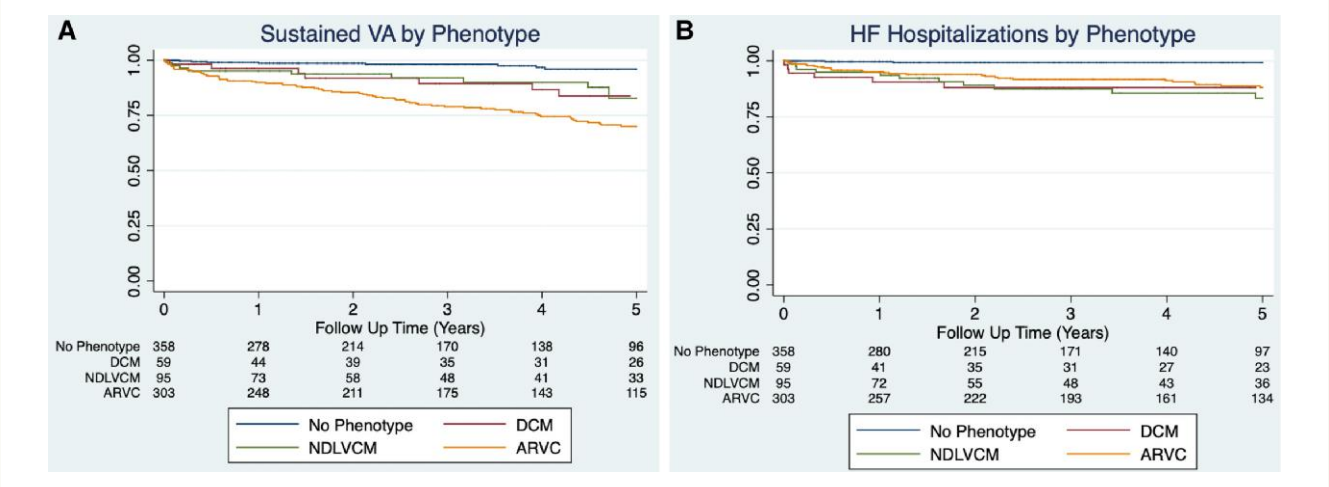


**Figure 1** Freedom from sustained VA (left panel) (overall log-rank $P < .001$) and from HF hospitalizations (right panel) (overall log-rank $P < .001$) of the study cohort stratified by the cardiomyopathy phenotype that was fulfilled. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HF, heart failure; VA, ventricular arrhythmia

(5) Episodes of myocardial injury were common (8.8%; 1.3%/year) and often recurred. Patients who experienced myocardial injury had an increased risk of arrhythmias and HF hospitalizations thereafter (HR 2.394 and 5.064, respectively).

## DSP cardiomyopathy—a case for a gene-specific approach?

The phenotypic expression of a cardiomyopathic disease is most often the first clinical finding appreciated during the evaluation of a new patient. The pattern-recognition based workflow of modern medicine has been deeply embedded with phenotypic features guiding diagnosis and patient management and forming the basis for established cardiomyopathy diagnostic criteria. While this phenotype-based paradigm has allowed for significant advances in patient diagnosis and management over the years, recent studies focusing on the role of genotype in cardiomyopathy have begun challenging it. Protonotarios *et al.*[9] showed compelling evidence that the reliability of arrhythmic risk assessment can vary dramatically depending on patients' underlying genetic substrate. Similarly, Paldino *et al.*[5] demonstrated the superiority of classifying patients according to underlying genotype rather than clinical phenotype for the purposes of predicting adverse arrhythmic events. Both studies thus suggest that genotype may provide greater utility for risk stratification of patients with arrhythmic cardiomyopathies.

Patients with P/LP *DSP* variants represent a population particularly well-suited to a gene-specific approach.[16] Consistent with prior publications, we found that the cardiomyopathy phenotype of these patients is heterogeneous, ranging from classical DCM, left-sided to biventricular ARVC, and the newer NDLVC designation (with or without systolic dysfunction), to phenotypes not captured fully by these currently accepted phenotypic classifications.[1,2,16,25,26] Patients with a known phenotype and a *DSP* P/LP variant had high rates of both VAs (2.7%–6.5%/year) and HF hospitalizations (2.1%–2.7%/year), confirming that patients with *DSP*-associated cardiomyopathy, regardless of the specific manifested phenotype, have a significant burden of disease. Our gene-specific enrolment strategy also allowed us to study individuals with P/LP *DSP* variants who did not fulfil any of these phenotype-based diagnoses. These genotype-positive phenotype-negative individuals comprised 32.5% of the study cohort. Their risk for sustained VA (incidence of 0.5%/year) and rapid, sustained VA (0.3%/year) was relatively low if compared to patients with a phenotype, but still not zero. Compared to the incidence of VA in historical cohorts of phenotype-negative plakophilin-2 carriers, for example, this event rate is notable.[27–29] These individuals may represent a significant challenge in management, as their rate of transition from phenotype negative to any of the current phenotypes (and therefore their associated risk) is still unclear. Similarly, the NDLVC phenotype includes patients with LGE but preserved LV function. Unsurprisingly, these patients have lower rates of HF than NDLVC patients with reduced systolic function. While arrhythmic risk may also be slightly lower in this group compared to those with reduced systolic function (1.9%/year vs. 3.6%/year), this difference did not reach statistical significance and larger studies are needed to fully address potential arrhythmic differences. It will be crucial to longitudinally assess disease progression and phenotype penetrance in future studies.

## Distinguishing the phenotypic features of DSP cardiomyopathy

In our study, patients harbouring P/LP *DSP* variants presented with increased TWI on ECG, had significant PVC burden (median 600 [17–2529]), a mildly reduced or borderline LVEF (49.5 ± 13.9%), preserved RV contraction (51.6 ± 10.6), and LV scarring/LGE seen at CMR (361/551, 65.5%, of which $n = 292$ was non-septal). This constellation of electrophysiological and structural features was associated with increased arrhythmogenicity and elevated risk for HF hospitalizations. In our view, these clinical findings (in combination with the presence of a P/LP *DSP* variant) thus represent the primary features of a distinct '*DSP* cardiomyopathy' phenotype and have the potential to serve as the basis for diagnostic criteria for this gene-specific entity.

In patients with *DSP* variants, electrophysiologic features were prominently associated with risk for both VA and HF hospitalizations. The risk of VAs climbed steadily with an increasing number of TWI on 12-lead ECG (3+ TWI, HR 2.149), and a strong logarithmic association with PVC burden was observed. Similar to the threshold used in the TFC for ARVC, 500+ PVC per 24 h was associated with a substantial increase in VA risk for patients with *DSP* cardiomyopathy as well

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**Table 4 Univariable outcome predictors**

| | Any VA event ($n = 139$) | | | Fast VA ($n = 69$) | | | HF hospitalization ($n = 72$) | | | LVAD/HTx/death ($n = 66$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Clinical characteristics ($n = 800$) | | | | | | | | | | | | |
| Age (/year) | 0.997 | 0.988–1.006 | .471 | 0.996 | 0.984–1.008 | .522 | 1.007 | 0.993–1.021 | .325 | 1.012 | 0.997–1.027 | .105 |
| Male sex | 0.698 | 0.490–0.996 | **.047** | 0.855 | 0.541–1.449 | .628 | 0.717 | 0.430–1.194 | .201 | 1.020 | 0.616–1.689 | .937 |
| Loss of function variant | 1.116 | 0.614–2.025 | .719 | 0.825 | 0.388–1.757 | .618 | 0.566 | 0.280–1.147 | .114 | 1.112 | 0.445–2.775 | .821 |
| Constitutive NMD-incompetent region ($n = 737$) | 0.627 | 0.405–0.973 | **.037** | 0.521 | 0.266–1.019 | *.057* | 0.807 | 0.445–1.466 | .483 | 1.089 | 0.605–1.959 | .777 |
| History of syncope | 1.527 | 1.024–2.276 | **.038** | 1.821 | 1.033–3.291 | **.038** | 1.388 | 0.762–2.528 | .283 | 1.110 | 0.564–2.185 | .762 |
| History of NSVT | 2.692 | 1.909–3.798 | **<.001** | 2.337 | 1.442–3.786 | **.001** | 1.491 | 1.026–2.741 | **.042** | 1.602 | 0.951–2.697 | *.076* |
| Previous sustained VA | 2.568 | 1.764–3.737 | **<.001** | 3.676 | 2.239–6.038 | **<.001** | 1.777 | 0.968–3.262 | *.063* | 3.415 | 2.043–5.711 | **<.001** |
| ECG parameters ($n = 782$) | | | | | | | | | | | | |
| PR ≥ 200 ms | 0.704 | 0.445–1.114 | .134 | 0.672 | 0.338–1.336 | .257 | 0.824 | 0.426–1.593 | .565 | 1.390 | 0.757–2.551 | .288 |
| TWI tot (/lead with TWI) | 1.108 | 1.047–1.173 | **<.001** | 1.058 | 0.975–1.148 | .176 | 1.161 | 1.084–1.244 | **<.001** | 1.035 | 0.939–1.141 | .488 |
| TWI ≥ 2 Inferior leads | 1.149 | 0.698–1.890 | .585 | 1.389 | 0.723–2.670 | .324 | 1.654 | 0.900–3.041 | .105 | 1.536 | 0.750–3.144 | .241 |
| TWI ≥ 3 precordial leads | 2.149 | 1.534–3.011 | **<.001** | 1.509 | 0.920–2.474 | .103 | 2.223 | 1.360–3.633 | **.001** | 1.507 | 0.912–2.491 | .109 |
| Holter parameters ($n = 534$) | | | | | | | | | | | | |
| PVC burden (log) | 1.278 | 1.160–1.407 | **<.001** | 1.181 | 1.034–1.348 | **.014** | 1.199 | 1.033–1.390 | **.016** | 1.073 | 0.884–1.302 | .476 |
| PVC burden (cont) | 1.000 | 1.000–1.001 | **.003** | 1.000 | 0.999–1.001 | *.056* | 1.000 | 1.000–1.001 | **.014** | 1.000 | 0.999–1.001 | .211 |
| PVC burden > 500 | 3.678 | 2.206–6.133 | **<.001** | 3.163 | 1.535–6.517 | **.002** | 2.161 | 1.076–4.340 | **.030** | 0.993 | .429–2.230 | .987 |
| Echocardiography parameters ($n = 709$) | | | | | | | | | | | | |
| LVEF (%) | 0.973 | 0.963–0.983 | **<.001** | 0.974 | 0.960–0.989 | **.001** | 0.945 | 0.931–0.961 | **<.001** | 0.908 | 0.889–0.927 | **<.001** |
| Moderate/severe RV dysfunction | 2.042 | 1.241–3.360 | **.005** | 1.688 | 0.846–3.288 | .138 | 1.376 | 0.624–3.033 | .429 | 2.289 | 1.157–4.528 | **.017** |
| Presence of RVWMA | 1.826 | 1.153–2.891 | **.010** | 1.346 | 0.722–2.511 | .350 | 1.282 | 0.573–2.865 | .546 | 1.571 | 0.711–3.473 | .264 |
| Presence of LVWMA | 1.822 | 1.291–2.572 | **.001** | 1.337 | 0.819–2.183 | .246 | 1.960 | 1.216–3.161 | **.006** | 2.367 | 1.388–4.039 | **.002** |
| CMR parameters ($n = 551$) | | | | | | | | | | | | |
| LVEDVi (/mL/m$^2$) | 1.012 | 1.005–1.019 | **<.001** | 1.015 | 1.006–1.024 | **.001** | 1.027 | 1.018–1.036 | **<.001** | 1.032 | 1.022–1.042 | **<.001** |
| LVEF (/%) | 0.959 | 0.945–0.972 | **<.001** | 0.951 | 0.932–0.971 | **<.001** | 0.933 | 0.914–0.951 | **<.001** | 0.905 | 0.878–0.933 | **<.001** |
| RVEDVi (/mL/m$^2$) | 1.002 | 0.996–1.008 | .506 | 1.003 | 0.995–1.011 | .436 | 1.002 | 0.993–1.012 | .611 | 1.006 | 0.993–1.018 | .397 |
| RVEF (/%) | 0.969 | 0.952–0.986 | **<.001** | 0.960 | 0.940–0.980 | **<.001** | 0.945 | 0.921–0.971 | **<.001** | 0.937 | 0.909–0.966 | **<.001** |
| Presence of RVWMA at CMR | 1.787 | 1.129–2.832 | **.013** | 1.175 | 0.615–2.243 | 0.626 | 1.683 | 0.813–3.481 | .161 | 1.655 | 0.636–4.307 | .302 |

*Continued*

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**Table 4** *Continued*

| | Any VA event (n = 139) | | | Fast VA (n = 69) | | | HF hospitalization (n = 72) | | | LVAD/HTx/death (n = 66) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P | HR | 95% CI | P | HR | 95% CI | P |
| Presence of LVWMA at CMR | 1.896 | 1.252–2.869 | **.002** | 1.240 | 0.689–2.232 | .473 | 3.009 | 1.540–5.881 | **.001** | 2.854 | 1.182–6.894 | **.020** |
| Presence of LGE | 1.738 | 1.094–2.760 | **.019** | 1.372 | 0.744–2.529 | .311 | 0.853 | 0.434–1.676 | .645 | 5.684 | 1.318–24.204 | **.020** |
| LV evaluation at combined CMR/Echo (n = 760) | | | | | | | | | | | | |
| Presence of LVWMA | 2.068 | 1.484–2.884 | **<.001** | 1.444 | 0.901–2.313 | .126 | 2.727 | 1.716–4.333 | **<.001** | 2.214 | 1.343–3.652 | **.002** |
| LVEF (/%) | 0.970 | 0.960–0.981 | **<.001** | 0.970 | 0.955–0.985 | **<.001** | 0.940 | 0.926–0.954 | **<.001** | 0.914 | 0.896–0.932 | **<.001** |
| LVEF ≤ 50 | 2.758 | 1.916–3.970 | **<.001** | 2.860 | 1.688–4.847 | **<.001** | 7.562 | 3.713–15.399 | **<.001** | 10.895 | 4.338–27.361 | **<.001** |
| LVEF ≤ 40 | 2.360 | 1.682–3.310 | **<.001** | 2.243 | 1.396–3.606 | **.001** | 5.713 | 3.385–9.642 | **<.001** | 9.758 | 5.028–18.936 | **<.001** |
| LVEF ≤ 35 | 2.049 | 1.440–2.916 | **<.001** | 2.223 | 1.358–3.639 | **.001** | 5.977 | 3.579–9.980 | **<.001** | 8.545 | 4.757–15.350 | **<.001** |
| LVEF ≤ 30 | 2.099 | 1.410–3.122 | **<.001** | 2.281 | 1.330–3.912 | **.003** | 4.620 | 2.755–7.747 | **<.001** | 9.518 | 5.507–16.450 | **<.001** |

*P* values < 0.05 have been bolded.
For the first three outcomes (any VA event; fast VA; and HF hospitalization), HRs are derived from a Fine–Grey model. For the fourth outcome (LVAD/HTx/Death), HRs are derived from a Cox regression model.
CMR, cardiac magnetic resonance; HTx, heart transplant; HF, heart failure; LGE, late gadolinium enhancement; LVAD, left ventricular assist device; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVWMA, left ventricular wall motion abnormality; NMD, nonsense mediated decay; NSVT, non-sustained ventricular tachycardia; P/LP, pathogenic/likely pathogenic; PVC, premature ventricular contraction; RV, right ventricular; RVEDVi, right ventricular end-diastolic volume index; RVWMA, right ventricular wall motion abnormality; TWI, T-wave inversion; VA, ventricular arrhythmia.

(HR 3.678). The presence of previous NSVT or prior sustained VA episodes (HR 2.692 and 2.568, respectively) was also strongly associated with the development of future sustained VA events.

Among the echocardiography- or CMR-derived morphological and functional features that were assessed as *DSP*-specific risk factors, there was overlap with established risk factors for DCM, NDLVC, and ARVC. Similar to DCM,[30] the presence of LGE on CMR was associated with a significant increase in risk of VAs in our cohort (HR 1.738). This corroborates previous findings suggesting that sub-epicardial LGE is a defining feature of *DSP* cardiomyopathy.[3,16] Similar to ARVC,[31] presence of RV dysfunction was also associated with an increase in VAs (moderate or severe dysfunction on echocardiogram, HR 2.042). In contrast, the importance of modest LV systolic dysfunction appeared specific to this patient population, with a LVEF ≤ 50% representing the main risk threshold (HR 2.758). With the exception of RV dysfunction on echocardiography, all morphologic predictors were strongly associated with HF hospitalizations as well, further confirming their role as important clinical features of this disease, although reduced LV function was the only independent HF risk factor in multivariable analysis.

Finally, the presence of myocardial injury episodes is both a distinguishing feature of *DSP* cardiomyopathy and has prognostic significance. The association between the presence of *DSP* variants and the incidence of myocardial injury/myocarditis has been previously described.[16,17,32,33] A recent study from Lota *et al.*[34] showed that around 8% of patients presenting with acute myocarditis harbour a pathogenic variant in one or more genes associated with arrhythmogenic cardiomyopathy, of which the most common was *DSP*. Our findings corroborate these previous reports, as 8.8% of the patients within our cohort experienced one or more myocardial injury episodes. As a novel finding, our study also demonstrated the clear prognostic importance of those episodes. Patients experiencing myocardial injury episodes subsequently had a more than two-fold increase in their arrhythmic risk and a more than five-fold increase in their risk for HF hospitalizations.

## Sex differences in DSP cardiomyopathy

Another unique, distinguishing feature of *DSP* cardiomyopathy is the high prevalence of female patients. Compared to large historical cohorts of patients with either DCM or ARVC phenotypes,[29,35] females were extensively represented across centres contributing to our study cohort. A similar preponderance of female patients has been consistently reported across *DSP* cohort studies.[16,17,22] In pooled meta-analyses, female sex has been found protective for risk of VA in ARVC and has a null effect in DCM,[31,36] although an exercise-associated confounder may exist, particularly for patients with classical ARVC.[37] In contrast, female patients with *DSP* variants, including those without prior arrhythmias, were at higher risk for VA compared to male patients (aHR for female sex: 1.548). The molecular and pathogenic reasons justifying this associations are yet to be fully decoded and differences in sex hormone levels and history of pregnancy may also play a role.[38] Further study on this topic would be critical to definitively understand the mechanism behind these biological differences.

## Clinical implications and future directions

Our data establish that *DSP* P/LP variants confer high risk of VA and SCD (including potentially life-threatening fast VA) and HF events. These results clearly support the recent ESC cardiomyopathy guidelines that consider *DSP* a 'high risk' gene.[24] The next goal of the *DSP*-ERADOS Network will be the development of a *DSP*-specific arrhythmic risk calculator encompassing the gene-specific features of risk described herein.

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**Table 5 Results from multivariable Cox regression in patients with electrocardiogram and echocardiography data available at first evaluation**

| Patients with ECG + echocardiography data at first evaluation ($n = 709$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any VA event ($n = 134$) | | | HF hospitalization ($n = 65$) | | | LVAD/HTx/Death ($n = 55$) | | |
| | aHR | 95% CI | *P* | aHR | 95% CI | *P* | aHR | 95% CI | *P* |
| Male sex | 0.646 | 0.441–0.947 | **.025** | | | | | | |
| History of NSVT | 1.721 | 1.143–2.564 | **.009** | 0.859 | 0.507–1.454 | .572 | 1.140 | 0.647–2.010 | .651 |
| Previous sustained VA | 1.923 | 1.205–3.069 | **.006** | 1.206 | 0.636–2.286 | .567 | 1.531 | 0.838–2.794 | .166 |
| History of syncope | 0.988 | 0.630–1.551 | .960 | | | | | | |
| ≥3 leads with TWI | 1.447 | 0.982–2.132 | .062 | 2.036 | 1.218–3.405 | **.007** | | | |
| LVEF ≤ 50% | 1.645 | 1.044–2.594 | **.032** | 3.879 | 2.012–7.474 | **<.001** | 8.742 | 3.325–22.981 | **<.001** |
| LVWMA | 1.095 | 0.721–1.663 | .670 | 1.167 | 0.707–1.926 | .547 | 1.102 | 0.634–1.912 | .731 |
| Presence of moderate/severe RV dysfunction | 1.458 | 0.781–2.722 | .237 | | | | 1.382 | 0.656–2.910 | .395 |
| RVWMA | 1.058 | 0.558–2.005 | .863 | | | | | | |

Only variables from the clinical characteristics, ECG parameters, and echocardiography parameters from *Table 4* reaching a $P < .10$ with the outcome of interest were included in the model. Although <.1 for any VA in *Table 4*, variant localization in an NMD region was not included in this model as it is limited to truncating/splice variants. A model including NMD region has been reported in Supplementary data online, *Table S9*. For TWI and LVEF, thresholds from Supplementary data online, *Figure S1* were used. *P* values < 0.05 have been bolded.
HF, heart failure; HTx, heart transplant; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVWMA, left ventricular wall motion abnormality; NMD, nonsense-mediated decay; NSVT, non-sustained ventricular tachycardia; RV, right ventricular; RVWMA, right ventricular wall motion abnormality; TWI, T-wave inversion; VA, ventricular arrhythmia.

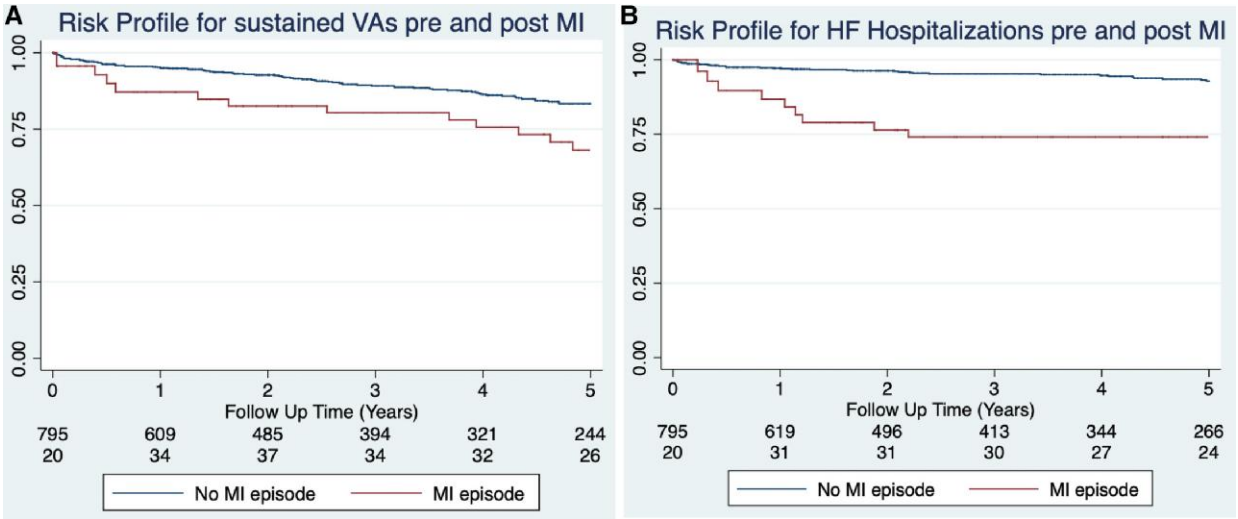


**Figure 2** Freedom from sustained VA events (upper panel) and from HF hospitalizations (lower panel) from patients for a patient population pre and post the occurrence of myocardial injury events. *X* axis reports time from first assessment (myocardial injury HR for VA: 2.394 [1.498–3.827], $P < .001$; for HF hospitalizations: 5.064 [2.847–9.004], $P < .001$). Number at risk for outcomes (VA events or HF hospitalizations) changes according to the time of occurrence of myocardial injury during follow-up time. HF, heart failure; MI, myocardial injury; VA, ventricular arrhythmia

Additionally, while these results suggest a gene-specific approach to risk stratification in *DSP* cardiomyopathy is needed, a truly genotype-specific approach has potential future benefit. For patients with *DSP* loss of function variants Hoorntje *et al.*[22] recently established that variant location associated with predicted susceptibility to NMD had prognostic implications for VA risk, a finding which was replicated in our sub-analysis (see Supplementary data online, *Table S9*), albeit with a lower effect size. Further research into genotype-specific outcomes within *DSP* cardiomyopathy as well as studies of the impact of genetic modifiers is on the horizon.

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## Limitations

This study was an international observational cohort study. The scope of the study was describing and characterizing the gene-specific risk features associated with *DSP* cardiomyopathy to help raise awareness of the specific features of this disease and aid clinicians in patient risk stratification for VA and HF. As in many early descriptions of genetic cardiovascular disease, our cohort of *DSP* P/LP variant carriers is likely biased towards patients and families with more severe disease expression.

Phenotypic characterization at the time of initial evaluation, particularly the use of CMR, was incomplete in this retrospective clinical cohort. We cannot exclude the possibility that the absence of phenotype in genotype-positive/phenotype-negative individuals, nearly half of whom lacked a CMR at baseline, could be related to incomplete diagnostic evaluation in those individuals. Additionally, some genotype-positive/phenotype-negative individuals had an ICD placed prior to initial evaluation. These individuals may have had cardiac pathology that fell outside of the typical diagnostic categories of *DSP*-related disease phenotype (e.g. ARVC, DCM, or NDLVC). Thus, while the incidence of sustained VA was low in this subgroup (0.5%/year), within the clinical setting a comprehensive evaluation should be performed prior to excluding the presence of *DSP*-related phenotype. The VA incidence in phenotype-negative individuals with comprehensive cardiovascular evaluations including a CMR may well be lower than 0.5%/year, but this requires further, ideally prospective, study. The high prevalence of missing CMR and Holter monitor data at baseline also limited direct comparability of the multivariable analyses presented in *Table 5* and Supplementary data online, *Tables S9–S11* due to different sub-cohorts.

Longitudinal electrophysiologic and imaging data reflecting disease progression during follow-up were not available for the present study. Thus, impact of dynamic changes in disease phenotype (e.g. a new drop in LVEF below 50%) that occur prior to arrhythmia or HF events is not captured in this analysis. Further longitudinal study of disease progression and its impact on DSP patient risk is warranted. Additionally, LGE presence was managed as a categorical variable as protocolized LGE quantification was unavailable. Likewise, while exercise could be a risk factor for disease expression and clinical outcomes in *DSP* cardiomyopathy given the well-known association with other forms of arrhythmogenic cardiomyopathy and ARVC,[39] granular exercise data were not available across participating centres. Finally, information regarding the pharmacologic management of specific outcomes, i.e. myocardial injury and HF episodes, were not routinely collected. We envision most of those specific questions to be addressed in the future by specifically tailored prospective studies.

# Conclusions

Patients harbouring P/LP *DSP* variants experience high rates of adverse events including sustained VA, HF hospitalization, and mortality. These patients demonstrate a distinct clinical phenotype (*DSP* cardiomyopathy) characterized by left ventricular fibrosis and systolic dysfunction, high burdens of ECG derangement and ventricular ectopy, and a higher arrhythmic risk in females.

Multiple electrophysiologic (prior NSVT or sustained VA events, PVC burden, number of TWI at 12-lead ECG) and morphologic/functional (LVEF ≤50%) characteristics were found to be associated with adverse events during follow-up in multivariable analysis. Inflammatory myocardial injury is a common, clinically significant event and causes an increase in patient risk for both VA and HF hospitalization. While of importance for the understanding of *DSP* cardiomyopathy, these results should be confirmed in a prospective study with standardized follow-up regimens. Additionally, further study of the implications of these findings as well as the development of gene-specific diagnostic and risk assessment tools are necessary to improve the care of patients with *DSP* cardiomyopathy.

# Supplementary data

Supplementary data are available at *European Heart Journal* online.

# Declarations

## Disclosure of Interest

L.M. is consultant for Tenaya, and received research funding from Pfizer, Greenstone Bio, and Tenaya. A.M.S. received educational grants through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, and Medtronic; and speaker/advisory board/consulting fees from Bayer Healthcare, Biotronik, Daiichi-Sankyo, Medtronic, Novartis, Pfizer, and Stride Bio Inc. H.C. is a consultant for Medtronic Inc., Biosense Webster, Pfizer, StrideBio, Abbott, and Tenaya. H.C. receives research support from Boston Scientific; C. Tichnell and C.A.J. receive salary support from this grant. C.A.J. receives research support from Lexeo, Inc. and StrideBio Inc.; C.A.J. is a consultant for Pfizer, Lexeo Therapeutics, and StrideBio, Inc. A.G. is a consultant for Lexeo. J.C.-T. is consultant for Tenaya, Lexeo, Bayer, and BMS/Pfizer. N.A.G. is a consultant for Kiniksa Pharmaceuticals. L.M. is consultant for Tenaya, and received research funding from Pfizer, Greenstone Bio, and Tenaya. A.S.J.M.t.R. and J.P.v.T. are consultants for StrideBio and Tenaya. G.S. is a consultant for Novartis, Impulse Dynamics, NovoNordisk, and Biotronik, and speaker and honoraria for Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini, and Ak-cea Therapeutics. M.M. is a consultant for Novartis, AstraZeneca, NovoNordisk, Pfizer, and Vitor Pharma. C.C. is a consultant for NovoNordisk and AstraZeneca. J.S.W. has received research support from Bristol-Myers Squibb, and advisory board/consultancy fees from Bristol-Myers Squibb, Foresite Labs, Pfizer, and Health Lumen. V.N.P. is on the Scientific Advisory Board for Lexeo Therapeutics. Authors for whom no specific disclosures are listed have nothing to disclose.

## Data Availability

To maintain patient confidentiality, data and study materials have not been made publicly available, but a limited data set may be made available upon request.

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## Ethical Approval

The study conforms to the Helsinki Declaration and was performed in accordance with regulations set forth by local institutional review/ethics boards.

## Pre-registered Clinical Trial Number

None supplied.

## 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**:1807–16. https://doi.org/10.1161/CIRCULATIONAHA.106.174287
2. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, *et al.* Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2007;**29**:270–6. https://doi.org/10.1093/eurheartj/ehm342
3. Augusto JB, Eiros R, Nakou E, Moura-Ferreira S, Treibel TA, Captur G, *et al.* Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study. *Eur Heart J Cardiovasc Imaging* 2020;**21**:326–36. https://doi.org/10.1093/ehjci/jez188
4. 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**:1480–90. https://doi.org/10.1016/j.jacc.2019.06.072
5. 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**:1981–94. https://doi.org/10.1016/j.jacc.2022.08.804
6. James CA, Gasperetti A. Genotype-based risk stratification can outperform phenotype-based practice for inherited cardiomyopathies. *J Am Coll Cardiol* 2022;**80**:1995–7. https://doi.org/10.1016/j.jacc.2022.09.018
7. Gigli M, Stolfo D, Graw SL, Merlo M, Gregorio C, Nee Chen S, *et al.* Phenotypic expression, natural history, and risk stratification of cardiomyopathy caused by filamin C truncating variants. *Circulation* 2021;**144**:1600–11. https://doi.org/10.1161/CIRCULATIONAHA.121.053521
8. Nishiuchi S, Makiyama T, Aiba T, Nakajima K, Hirose S, Kohjitani H, *et al.* Gene-based risk stratification for cardiac disorders in LMNA mutation carriers. *Circ Cardiovasc Genet* 2017;**10**:e001603. https://doi.org/10.1161/CIRCGENETICS.116.001603
9. Protonotarios A, Bariani R, Cappelletto C, Pavlou M, García-García A, Cipriani A, *et al.* Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J* 2022;**43**:3053–67. https://doi.org/10.1093/eurheartj/ehac235
10. Verstraelen TE, van Lint FHM, Bosman LP, de Brouwer R, Proost VM, Abeln BGS, *et al.* Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers—reaching the frontiers of individual risk prediction. *Eur Heart J* 2021;**42**:2842–50. https://doi.org/10.1093/eurheartj/ehab294
11. Smith EA, Fuchs E. Defining the interactions between intermediate filaments and desmosomes. *J Cell Biol* 1998;**141**:1229–41. https://doi.org/10.1083/jcb.141.5.1229
12. Rampazzo A, Nava A, Malacrida S, Beffagna G, Bauce B, Rossi V, *et al.* Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2002;**71**:1200–6. https://doi.org/10.1086/344208
13. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, *et al.* An international evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) using the ClinGen framework. *Circ Genom Precis Med* 2021;**14**:e003273. https://doi.org/10.1161/CIRCGEN.120.003273
14. 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
15. Gasperetti A, Peretto G, Muller SA, Hasegawa K, Compagnucci P, Casella M, *et al.* Catheter ablation for ventricular tachycardia in patients with desmoplakin cardiomyopathy. *JACC Clin Electrophysiol* 2024;**10**:487–98. https://doi.org/10.1016/j.jacep.2023.11.017
16. Smith ED, Lakdawala NK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, *et al.* Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2020;**141**:1872–84. https://doi.org/10.1161/CIRCULATIONAHA.119.044934
17. Wang W, Murray B, Tichnell C, Gilotra NA, Zimmerman SL, Gasperetti A, *et al.* Clinical characteristics and risk stratification of desmoplakin cardiomyopathy. *Europace* 2021;**24**:268–77. https://doi.org/10.1093/europace/euab183
18. Di Lorenzo F, Marchionni E, Ferradini V, Latini A, Pezzoli L, Martino A, *et al.* DSP-related cardiomyopathy as a distinct clinical entity? Emerging evidence from an Italian cohort. *Int J Mol Sci* 2023;**24**:2490. https://doi.org/10.3390/ijms24032490
19. Gasperetti A, Carrick R, Protonotarios A, Laredo M, Van Der Schaaf I, Syrris P, *et al.* Long-term arrhythmic follow-up and risk stratification of patients with desmoplakin-associated arrhythmogenic right ventricular cardiomyopathy. *JACC Adv* 2024;**3**:100832. https://doi.org/10.1016/j.jacadv.2024.100832
20. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al.* 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**:405–24. https://doi.org/10.1038/gim.2015.30
21. Van Lint FHM, Murray B, Tichnell C, Zwart R, Amat N, Lekanne Deprez RH, *et al.* Arrhythmogenic right ventricular cardiomyopathy-associated desmosomal variants are rarely de novo: segregation and haplotype analysis of a multinational cohort. *Circ Genom Precis Med* 2019;**12**:e002467. https://doi.org/10.1161/CIRCGEN.119.002467
22. Hoorntje ET, Burns C, Marsili L, Corden B, Parikh VN, te Meerman GJ, *et al.* Variant location is a novel risk factor for individuals with arrhythmogenic cardiomyopathy due to a desmoplakin (DSP) truncating variant. *Circ Genom Precis Med* 2023;**16**:e003672. https://doi.org/10.1161/CIRCGEN.121.003672
23. 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. *Eur Heart J* 2010;**31**:806–14. https://doi.org/10.1093/eurheartj/ehq025
24. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.* 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–626. https://doi.org/10.1093/eurheartj/ehad194
25. Protonotarios A, Cannie D, Akhtar M, Savvatis K, Sekhri N, Mohiddin S, *et al.* Exploring the phenotypic spectrum of desmoplakin cardiomyopathy. *Eur Heart J* 2020;**41**:ehaa946.2053. https://doi.org/10.1093/ehjci/ehaa946.2053
26. 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
27. te Riele ASJM, James CA, Rastegar N, Bhonsale A, Murray B, Tichnell C, *et al.* Yield of serial evaluation in at-risk family members of patients with ARVD/C. *J Am Coll Cardiol* 2014;**64**:293–301. https://doi.org/10.1016/j.jacc.2014.04.044
28. te Riele ASJM, Bhonsale A, James CA, Rastegar N, Murray B, Burt JR, *et al.* Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 2013;**62**:1761–9. https://doi.org/10.1016/j.jacc.2012.11.087
29. Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, *et al.* Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet* 2015;**8**:437–46. https://doi.org/10.1161/CIRCGENETICS.114.001003
30. Di Marco A, Brown PF, Bradley J, Nucifora G, Claver E, de Frutos F, *et al.* Improved risk stratification for ventricular arrhythmias and sudden death in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2021;**77**:2890–905. https://doi.org/10.1016/j.jacc.2021.04.030
31. Bosman LP, Sammani A, James CA, Cadrin-Tourigny J, Calkins H, van Tintelen JP, *et al.* Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *Heart Rhythm* 2018;**15**:1097–107. https://doi.org/10.1016/j.hrthm.2018.01.031
32. Poller W, Haas J, Klingel K, Kühnisch J, Gast M, Kaya Z, *et al.* Familial recurrent myocarditis triggered by exercise in patients with a truncating variant of the desmoplakin gene. *J Am Heart Assoc* 2020;**9**:e015289. https://doi.org/10.1161/JAHA.119.015289
33. Kissopoulou A, Fernlund E, Holmgren C, Isaksson E, Karlsson J, Green H, *et al.* Monozygotic twins with myocarditis and a novel likely pathogenic desmoplakin gene variant. *ESC Heart Fail* 2020;**7**:1210–6. https://doi.org/10.1002/ehf2.12658

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34. Lota AS, Hazebroek MR, Theotokis P, Wassall R, Salmi S, Halliday BP, *et al.* Genetic architecture of acute myocarditis and the overlap with inherited cardiomyopathy. *Circulation* 2022;**146**:1123–34. https://doi.org/10.1161/CIRCULATIONAHA.121.058457
35. Escobar-Lopez L, Ochoa JP, Royuela A, Verdonschot JAJ, Ferro D, Espinosa M, *et al.* Clinical risk score to predict pathogenic genotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2022;**80**:1115–26. https://doi.org/10.1016/j.jacc.2022.06.040
36. Sammani A, Kayvanpour E, Bosman LP, Sedaghat-Hamedani F, Proctor T, Gi W, *et al.* Predicting sustained ventricular arrhythmias in dilated cardiomyopathy: a meta-analysis and systematic review. *ESC Heart Fail* 2020;**7**:1430–41. https://doi.org/10.1002/ehf2.12689
37. Rootwelt-Norberg C, Lie ØH, Chivulescu M, Castrini AI, Sarvari SI, Lyseggen E, *et al.* Sex differences in disease progression and arrhythmic risk in patients with arrhythmogenic cardiomyopathy. *Europace* 2021;**23**:1084–91. https://doi.org/10.1093/europace/euab077
38. Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, *et al.* Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. *Eur Heart J* 2017;**38**:1498–508. https://doi.org/10.1093/eurheartj/ehx011
39. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith HJ, *et al.* Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail* 2014;**16**:1337–44. https://doi.org/10.1002/ejhf.181

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