Prevalence and prognostic impact of pathogenic variants in patients with dilated cardiomyopathy referred for ventricular tachycardia ablation

Ebert, M.; Wijnmaalen, A.P.; Riva, M. de; Trines, S.A.; Androulakis, A.F.A.; Glashan, C.A.; ... ; Zeppenfeld, K.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 6, NO. 9, 2020

PUBLISHED BY ELSEVIER

Prevalence and Prognostic Impact of Pathogenic Variants in Patients With Dilated Cardiomyopathy Referred for Ventricular Tachycardia Ablation

Micaela Ebert, MD,[a] Adrianus P. Wijnmaalen, MD, PhD,[a] Marta de Riva, MD,[a] Serge A. Trines, MD, PhD,[a] Alexander F.A. Androulakis, MD,[a] Claire A. Glashan, MD,[a] Martin J. Schalij, MD, PhD,[a] J. Peter van Tintelen, MD, PhD,[b,c] Jan D.H. Jongbloed, MSc, PhD,[d] Katja Zeppenfeld, MD, PhD[a]

ABSTRACT

OBJECTIVES This study aimed to assess the frequency of (likely) pathogenic variants (LP/P*v*) among dilated cardiomyopathy (DCM) ventricular tachycardia (VT) patients referred for CA and their impact on procedural outcome and long-term prognosis.

BACKGROUND The prevalence of genetic variants associated with monomorphic VT among DCM is unknown.

METHODS Ninety-eight consecutive patients (age 56 ± 15 years; 84% men, left ventricular ejection fraction [LVEF] 39 ± 12%) referred for DCM-VT ablation were included. Patients underwent electroanatomical mapping and testing of ≥55 cardiomyopathy-related genes. Mapping data were analyzed for low-voltage areas and abnormal potentials. LP/P*v*-positive (LP/P*v*+) patients were compared with LP/P*v*-negative (LP/P*v*–) patients and followed for VT recurrence and mortality.

RESULTS In 37 (38%) patients, LP/P*v* were identified, most frequently *LMNA* (n = 11 of 37, [30%]), *TTN* (n = 6 of 37, [16%]), *PLN* (n = 6 of 37, [16%]), *SCN5A* (n = 3 of 37, [8%]), *RBM20* (n = 2 of 37, [5%]) and *DSP* (n = 2 of 37, [5%]). LP/P*v*+ carriers had lower LVEF (35 ± 13% vs. LP/P*v*–: 42 ± 11%; p = 0.005) and were less often men (n = 27 [73%] vs. n = 55 [90%]; p = 0.03). After a median follow-up of 2.4 years (interquartile range: 0.9 to 4.4 years), 63 (64%) patients had VT recurrence (LP/P*v*+: 30 of 37 [81%] vs. LP/P*v*–: 33 of 61 [54%]; p = 0.007). Twenty-eight patients (29%) died (LP/P*v*+: 19 of 37 [51%] vs. LP/P*v*–: 9 of 61 [15%]; p < 0.001). The cumulative 2-year VT-free survival was 41% in the total cohort (LP/P*v*+: 16% vs. LP/P*v*–: 54%; p = 0.001). The presence of LP/P*v* (hazard ratio: 1.9; 95% confidence interval: 1.1 to 3.4; p = 0.02) and unipolar low-voltage area size/cm^2 increase (hazard ratio: 2.5; 95% confidence interval: 1.6 to 4.0; p < 0.001) were associated with a decreased 2-year VT-free survival.

CONCLUSIONS In patients with DCM-VT, a genetic cause is frequently identified. LP/P*v*+ patients have a lower LVEF and more extensive VT substrates, which, in combination with disease progression, may contribute to the poor prognosis. Genetic testing in patients with DCM-VT should therefore be recommended. (J Am Coll Cardiol EP 2020;6:1103–14)

From the [a]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [b]Department of Clinical Genetics, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [c]Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands; and the [d]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. This work was supported by the Dutch Heart Foundation (CVON2015-12 eDETECT and 2018-30 PREDICT [to Dr. van Tintelen]). The Department of Cardiology Leiden has received research and fellowship grants from Edward Lifesciences, Boston Scientific, Medtronic, Biotronik, and Biosense Webster. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received January 3, 2020; revised manuscript received April 13, 2020, accepted April 20, 2020.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2020.04.025

ABBREVIATIONS AND ACRONYMS

AS = anteroseptal

CA = catheter ablation

DCM = dilated cardiomyopathy

EAVM = electroanatomical voltage mapping

ICD = implantable cardioverter-defibrillator

IL = inferolateral

LP/P*v* = likely pathogenic or pathogenic variant

LP/P*v*+ = likely pathogenic or pathogenic variant-positive

LP/P*v*– = likely pathogenic or pathogenic variant-negative

LV = left ventricular

LVA = low-voltage area

MSVT = monomorphic sustained ventricular tachycardia

Catheter ablation (CA) for drug-refractory ventricular tachycardia (VT) in patients with dilated cardiomyopathy (DCM) is being increasingly performed (1). However, VT recurrence after ablation is higher than in ischemic cardiomyopathy (2), and multiple procedures are often required (3). Historically, DCM has been defined by left ventricular (LV) dilatation and LV systolic dysfunction in the absence of abnormal loading conditions and coronary artery disease (4). The DCM phenotype is, however, an umbrella term that includes several genetic and acquired etiologies, which may impact both the VT substrate and outcome of ablation (5). Of importance, outcome data after DCM-VT ablation arises from mixed cohorts, in which the proportion of patients with specific etiologies is unknown (2,3,6,7). The rapid development of genetic testing has led to the identification of pathogenic variants associated with DCM and ventricular arrhythmias of different mechanisms (8–10). Frequent occurrence of monomorphic sustained VT (MSVT) has only been reported in *LMNA* variant carriers. Outcome data after CA in this patient population report high recurrence rates and poor transplant-free survival (11,12). In this respect, early identification of other high-risk subgroups among DCM patients presenting with MSVT would be desirable. However, according to currently available guidelines, genetic testing should be reserved for patients with suspected familial DCM or in DCM with specific clinical presentation such as conduction disease but not specifically in those presenting with MSVT (5,13–17).

Data on the prevalence of genetic DCM in patients with MSVT and the impact of different likely pathogenic or pathogenic variants (LP/P*v*) on VT ablation outcome are scarce. In the current study, we aimed to: 1) assess the prevalence of LP/P*v* (class 4 or 5) (18) in consecutive patients with DCM and MSVT referred for CA; 2) investigate the association between different genetic variants and the arrhythmogenic substrate location; and 3) assess the impact of LP/P*v* on procedural outcome and long-term prognosis.

SEE PAGE 1115

METHODS

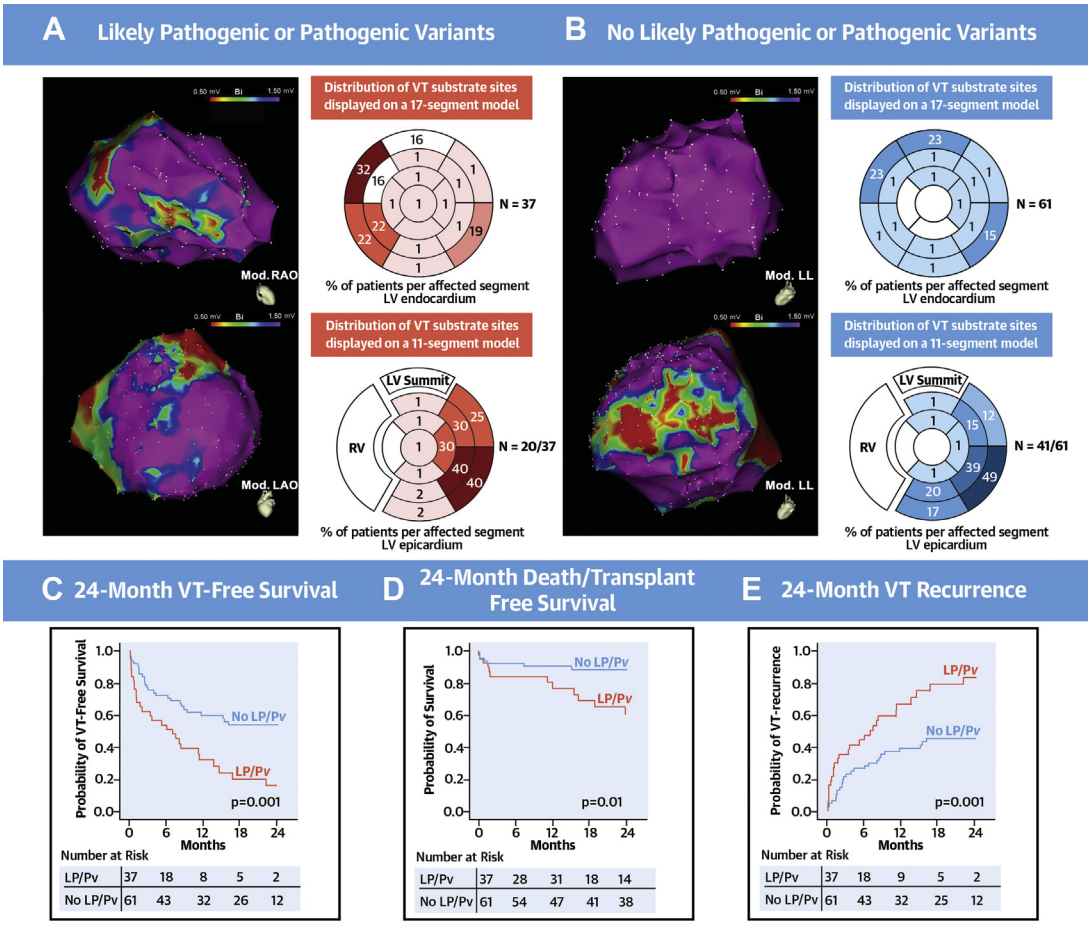
PATIENT POPULATION. Between January 2008 and August 2018, 468 patients with MSVT and a predominantly left-sided cardiomyopathy were referred for ablation to our center. All patients had LV dysfunction or evidence of myocardial scar on cardiac imaging (echocardiography or contrast-enhanced cardiac magnetic resonance [CE-CMR]) or on electroanatomical voltage mapping [EAVM]). Patients with significant coronary artery disease (defined by the presence of >75% coronary stenosis) and a myocardial scar corresponding to the perfusion area supplied by the stenotic coronary artery were excluded. In addition, patients with congenital heart disease, hypertrophic or restrictive cardiomyopathy, biopsy-proven myocarditis, cardiac sarcoidosis, LV non-compaction, or primary valvular disease were excluded. The final study population consisted of patients with idiopathic DCM (iDCM). A schematic of the patient selection process is shown in Supplemental Figure 1. All patients were treated according to routine clinical protocol and provided informed consent for the procedure. The Dutch Central Committee on Human-related Research permits use of anonymous data without prior approval of an Institutional Review Board if the data are obtained for patient care and do not contain identifiers that could be traced back to the individual patient.

GENETIC EVALUATION. Genetic counseling was offered to all patients. The family history of cardiomyopathies and sudden cardiac death before 50 years of age was obtained and familial DCM was defined as the presence of ≥2 closely related family members (first- and second-degree relatives) with iDCM (5,19).

Genetic testing by combined next-generation and Sanger sequencing of ≥55 cardiomyopathy-related genes became available in 2012 and was performed in all patients thereafter. Forty patients were ablated before 2012. Of those, 20 were tested for genetic variants during follow-up. The remaining 20 patients did not undergo genetic testing (refused or distant place of residence [n = 9], or died [n = 11] before being approached for genetic testing) and were excluded from the study. A list of the target genes is shown in Supplemental Table 1. All variants were reclassified according to the most recent available data in February 2019.

PRE-PROCEDURAL EVALUATION. In all patients, a comprehensive evaluation was performed aiming to identify underlying DCM etiologies. Medical records were reviewed for arrhythmias and failed antiarrhythmic drugs (AADs). Implantable cardioverter-defibrillator (ICD) recordings and 12-lead electrocardiograms were reviewed to identify (presumed) clinical VTs. Evaluation of cardiac function and scar delineation was performed based on echocardiography or CE-CMR. A coronary angiogram or a

CENTRAL ILLUSTRATION Substrate Locations and Long-Term Outcomes



Ebert, M. et al. J Am Coll Cardiol EP. 2020;6(9):1103–14.

Substrate location according to the presence of likely pathogenic or pathogenic variants (LP/P*v*) and Kaplan-Meier estimates comparing 24-month ventricular tachycardia (VT)–free survival, all-cause death or transplant-free survival, and the probability of 24-month VT recurrence according to the presence or absence of LP/P*v*. The locations of the VT substrates targeted by ablation were analyzed per segment and displayed on a 17- or 11-segment model for the left ventricular (LV) endocardium or epicardium. Bull's-eye plots depict the presence and location of (presumed) VT substrates targeted by ablation in **(A)** LP/P*v*-positive patients or **(B)** LP/P*v*-negative patients. Kaplan-Meier estimates comparing **(C)** 24-month VT-free survival, **(D)** death or transplant-free survival, and **(E)** the probability of 24-month VT recurrence. RV = right ventricular.

coronary computed tomography (CT) was performed to exclude significant coronary artery disease. In case of epicardial ablation, electrocardiography-gated CT-derived images were used for procedural integration as previously described (20). All AADs (except for amiodarone) were discontinued prior to the ablation.

PROCEDURAL STRATEGY. Endocardial mapping was performed in all patients, and epicardial mapping was performed in case of prior endocardial ablation failure or evidence of epicardial scar on CE-CMR. An epicardial access was not attempted in case of prior cardiac surgery or when limited substrate accessibility because of overlying anatomical structures such as coronary arteries or basal fat layer were anticipated in the presence of a basal, anteroseptal (AS) VT substrate (21). If a combined endocardial or epicardial ablation remained ineffective for controlling VT, additional strategies were applied, including escalation of AADs (defined as increase of amiodarone dosage or combination with Class I AADs), bipolar

ablation, or multidisciplinary interventional procedures such as CA with the support of extracorporeal membrane oxygenation, transcoronary ethanol ablation, percutaneous CA facilitated by a surgical epicardial window, or surgical cryoablation.

ELECTROANATOMICAL MAPPING AND ABLATION. The procedure was performed under conscious or deep sedation or general anesthesia, when indicated. Prior to ablation, programmed electrical stimulation was conducted (4 drive cycle lengths [600, 500, 400, and 350 ms], up to 4 extrastimuli until ventricular effective refractory period, from 2 right ventricular sites and 1 LV site). Positive endpoint of stimulation was induction of MSVT lasting ≥30 s or requiring termination owing to hemodynamic compromise.

All patients underwent 3-dimensional high-density (fill threshold ≤15 mm) EAVM of the LV endocardium. In addition, the right ventricle or the epicardium were mapped when deemed appropriate. Bipolar voltage maps were created using a 3.5-mm irrigated-tip catheter (NaviStar Thermocool; Biosense Webster, Diamond Bar, California) and the CARTO (Biosense Webster) system. Standard cutoff values of 1.5 mV and 8.01 mV were used to define bipolar and unipolar low-voltage areas (LVAs), respectively (21). LVAs with abnormal electrograms consistent with conduction delay (split, late, or fragmented potentials) were considered potential substrates for VT. In addition, hemodynamically tolerated VTs were approached by activation or entrainment mapping to identify presumptive VT-related and critical isthmus sites. For nonmappable VTs, pace mapping was performed in addition to substrate mapping. Radiofrequency energy was delivered up to 50 W with a temperature limit of 43°C and flow rates of 20 to 30 ml/min.

ACUTE PROCEDURAL OUTCOME. After the ablation, the entire induction protocol was repeated. Non-inducibility of any MSVT was considered as complete acute success, with persistent inducibility of any nonclinical VT as partial success. Inducibility of the (presumed) clinical VT after ablation was defined as procedural failure. If multiple procedural attempts were considered appropriate to control the arrhythmias (including bailout interventions), acute and long-term outcomes were assessed after the last (endo- or epicardial or bailout) procedure.

ANALYSIS OF ELECTROANATOMICAL SUBSTRATE. Unipolar and bipolar LVA were manually traced using integrated CARTO software. In addition, electrograms consistent with slow conduction as well as VT-related sites were tagged on the map. For each patient, the VT substrate, as defined previously, was displayed on a bull's-eye image containing 17 segments (with the aorta, mitral valve, and apex as references) for the LV endocardium and 11 segments for the epicardium (excluding the right ventricular and LV summit) (6). For each patient, the affected segments in the endocardium and epicardium (if available) were determined. Based on the predominantly involved segments within the LV, substrates were categorized as AS or inferolateral (IL). Subsequently, the total number of affected segments of all patients was displayed color-coded on the 17- and 11-segment models (**Central Illustration**).

FOLLOW-UP AND OUTCOMES. Patients were followed in the outpatient clinic, including ICD interrogation 2 months after ablation and at 6-month intervals thereafter. VT recurrence was defined as occurrence of any sustained VT (lasting >30 s) recorded on ICD or 12-lead electrocardiography. The dead-or-alive status of patients was checked via a query on the national Personal Records Database. The Personal Records Database contains personal data of people who live in the Netherlands and of Dutch citizens who live abroad. For patients followed at other institutions or in case of death, the referring hospital or physician was contacted for VT recurrence and cause of death. Long-term outcomes included: 1) VT recurrence; 2) heart transplantation (HTx) or LV assist device (LVAD)-free survival; and 3) survival free of any VT or death.

STATISTICAL ANALYSIS. Categorical variables are reported as number and percentage, and continuous variables are presented as mean ± SD when normally distributed or median (interquartile range [IQR]) when not normally distributed. Continuous variables were compared with the Student's *t*-test and categorical variables with chi-square test or Fisher exact test when applicable. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Univariable Cox proportional hazards analysis was used to test the association between the outcome event (2-year VT-free survival) and baseline covariates. The combined endpoint of VT recurrence or death or HTx was defined as dependent variable. Only variables with p values <0.10 at univariable analysis and age were included in the model for multivariable analysis. All tests were 2-sided, and a p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, New York).

TABLE 1 Baseline Characteristics of Patients Undergoing VT Ablation

	Total (N = 98)	LP/Pv+ (n = 37)	LP/Pv- (n = 61)	p Value*
Family history				
Familial DCM	15 (15)	10 (27)	5 (8)	0.01
Positive family history of SCD (%)	24 (25)	13 (35)	11 (18)	0.06
Patient characteristics				
Male	82 (84)	27 (73)	55 (90)	0.03
Age, yrs	56 ± 15	55 ± 16	57 ± 14	0.70
NYHA functional class				
I	43 (44)	11 (30)	32 (53)	0.03
II	35 (36)	16 (43)	19 (31)	0.20
III or IV	20 (20)	9 (24)	11 (18)	0.50
LVEF, %	39 ± 12	35 ± 13	42 ± 11	0.005
LVEF ≥50%	22 (22)	5 (14)	17 (28)	0.10
LVEF ≥35%	63 (64)	18 (49)	45 (74)	0.01
LVEDD, mm	61 ± 8	63 ± 9	60 ± 7	0.05
LVEDD ≤59 mm	38 (39)	16 (40)	22 (38)	0.80
CE-CMR	58 (59)	16 (43)	41 (69)	0.01
Presence of LGE	46/58 (79)	12/16 (75)	34/42 (81)	0.60
History of AF	35 (36)	17 (46)	18 (30)	0.10
Diabetes mellitus	13 (13)	9 (24)	4 (7)	0.01
Hypertension	31 (32)	12 (32)	19 (31)	0.90
COPD	8 (8)	6 (16)	2 (3)	0.02
eGFR, ml/min/1.73 m^2	64 ± 16	63 ± 17	64 ± 16	0.80
Medication				
ACE inhibitor/AT1	68 (69)	28 (76)	40 (66)	0.30
ARB	30 (31)	14 (38)	16 (26)	0.30
β-blocker	64 (65)	28 (76)	36 (59)	0.09
Calcium antagonist	2 (2)	0 (0)	2 (3)	0.30
Failed AAD†	79 (81)	32 (87)	47 (77)	0.30
Class I	26 (27)	6 (16)	20 (33)	0.07
Sotalol	29 (30)	10 (27)	19 (31)	0.50
Amiodarone	43 (44)	21 (57)	22 (36)	0.05
Type of device present				
None	19 (19)	1 (3)	18 (30)	0.001
CRT-D or CRT-P	34 (35)	17 (46)	17 (28)	0.07
ICD only	51 (52)	21 (57)	30 (49)	0.50

Values are n (%), mean ± SD, or n/N (%). The p value refers to the comparison between LP/Pv+ vs. LP/Pv- patients. †Excluding β-blockers.

AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; AT1 = angiotensin type 1 receptor blocker; CL = cycle length; CE-CMR = contrast-enhanced cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-D = cardiac resynchronization therapy with pacemaker; DCM = dilated cardiomyopathy; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LP/Pv+ = likely pathogenic or pathogenic variant positive; LP/Pv- = likely pathogenic or pathogenic variant negative; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.

TABLE 2 EAM and Procedural Data

	Total (N = 98)	LP/Pv+ (n = 37)	LP/Pv- (n = 61)	p Value
EAM findings				
LV endocardial mapping	98 (100)	37 (100)	61 (100)	–
Surface, cm^2	178 (154–211)	191 (160–217)	172 (146–210)	0.10
Map density, points/cm^2	1.2 (0.9–1.5)	1.3 (0.9–1.6)	1.2 (0.9–1.5)	0.30
Bipolar LVA <1.5 mV, cm^2	5 (0–15)	7 (0–21)	2 (0–14)	0.10
Unipolar LVA <8.01 mV, cm^2	43 (12–86)	71 (33–130)	34 (10–78)	0.004
Presence of any abnormal EGMs	72 (74)	31 (84)	41 (67)	0.07
RV endocardial mapping	44 (45)	21 (57)	23 (38)	0.07
Epicardial mapping	61 (62)	20 (54)	41 (67)	0.20
Map density, points/cm^2	0.9 (0.8–1.3)	0.9 (0.8–1.6)	0.9 (0.8–1.3)	0.30
Presence of any abnormal EGMs	51 (84)	18/20 (90)	32/41 (81)	0.60
Anteroseptal substrate	48 (49)	22 (60)	26 (43)	0.10
Inferolateral substrate	50 (51)	15 (40)	35 (57)	0.10
Procedural data				
Mean CL induced VTs, ms	334 ± 86	354 ± 91	323 ± 81	0.09
VT hemodynamically tolerated	25 (26)	7 (19)	18 (30)	0.30
RF time, min	14 ± 12	18 ± 15	12 ± 9	0.03
RF endocardial	66 (67)	25 (68)	41 (67)	1.00
RF epicardial (% of epicardial maps)	45 (74)	16 (81)	29 (71)	0.40
Fluoroscopy time, min	56 ± 25	58 ± 28	55 ± 22	0.50
Procedural duration, min	286 ± 102	286 ± 100	286 ± 102	1.00

Values are n (%), median (interquartile range), or mean ± SD.

EGM = electrogram; LVA = low-voltage area; RF = radiofrequency; RV = right ventricular; other abbreviations as in Table 1.

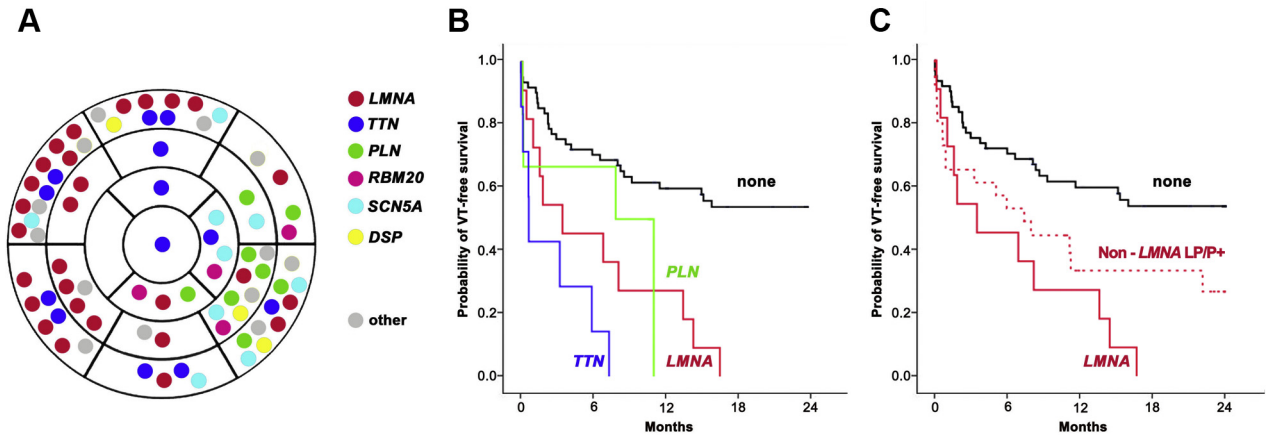
RESULTS

PATIENT CHARACTERISTICS AND GENETIC TESTING. Ninety-eight consecutive patients with iDCM referred for MSVT ablation (84% men, 56 ± 15 years of age) were included. Thirty-eight (39%) patients presented with VT storm (≥3 ICD shocks per 24 h) or incessant VT. Fifty-three (54%) patients were referred for CA shortly after the first episode(s) of MSVT: 33 (34%) within the first year and 20 (20%) within the second year. Thirty-two (33%) patients had previously undergone an endocardial VT ablation attempt (n = 29 of 32 [91%] at another center). Of those 12 of 32 (37%) patients died and 20 of 32 (63%) were alive at the end of follow-up (p = 0.2)

A positive family history for DCM or sudden cardiac death was present in 15 (15%) and 24 (25%) patients, respectively. The mean LV ejection fraction (LVEF) was 39 ± 12%. In 46 of 58 (79%) patients in whom a CE-CMR was available, a myocardial scar was detected and coincided with electroanatomical LVA. Table 1 depicts the baseline characteristics of the study population at the time of admission for ablation.

In 37 (38%) patients, an LP/Pv was identified. Supplemental Table 2 provides details of the LP/Pv. The most frequent LP/Pv were found in the *LMNA* gene (n = 11 of 37 [30%]), followed by *TTN* (n = 6 of 37 [16%]), *PLN* (n = 6 of 37 [16%]), *SCN5A* (n = 3 of 37 [8%]), *RBM20* (n = 2 of 37 [5%]), and *DSP* (n = 2 of 37 [5%]). Variants of unknown significance

FIGURE 1 Substrate Locations Related to Distinct Genetic Variants



(A) Substrate locations related to distinct genetic variants and **(B)** impact of most frequent likely pathogenic or pathogenic variants on 24-month ventricular tachycardia (VT)-free survival. **(C)** Impact of *LMNA* variants compared with all other likely pathogenic or pathogenic variants on 24-month VT-free survival.

were detected in 21 (21%) patients and grouped together with the patients with negative genetic testing. A positive family history for DCM was more often present LP/P*v*-positive (LP/P*v*+) patients versus LP/P*v*-negative ((LP/P*v*-) patients (n = 10 of 37 [27%] vs. n = 5 of 61 [8%]; p = 0.01). Although not reaching statistical significance, there was a tendency toward a more frequent positive family history for sudden cardiac death among LP/P*v*+ patients (13 of 37 [35%] vs. 11 of 61 [18%]; p = 0.06).

ELECTROANATOMICAL MAPPING. High-density LV endocardial mapping was performed in all patients, epicardial mapping in 61 (62%), and right ventricular (septal) mapping in 44 (45%) patients. Of importance, LP/P*v*+ patients had similar endocardial bipolar but larger unipolar LVA than LP/P*v*- patients (7 cm^2 [IQR: 0 to 21 cm^2] and 71 cm^2 [IQR: 33 to 130 cm^2] vs. 2 cm^2 [IQR: 0 to 14 cm^2] and 34 cm^2 [IQR: 10 to 78 cm^2]; p = 0.10 and p = 0.004, respectively). Details about EAVM and procedural data are shown in Table 2.

In total, 387 VTs were induced (median 3 [IQR: 1 to 5] per patient). LP/P*v*+ patients had a similar number of VTs to LP/P*v*- patients (median 2 [2 to 5] per patient vs. 3 [1 to 5] per patient; p = 0.40), and (limited) activation or entrainment mapping was possible for ≥1 VT in 60 (61%) patients. Remaining VTs were targeted by a combination of substrate and pace mapping.

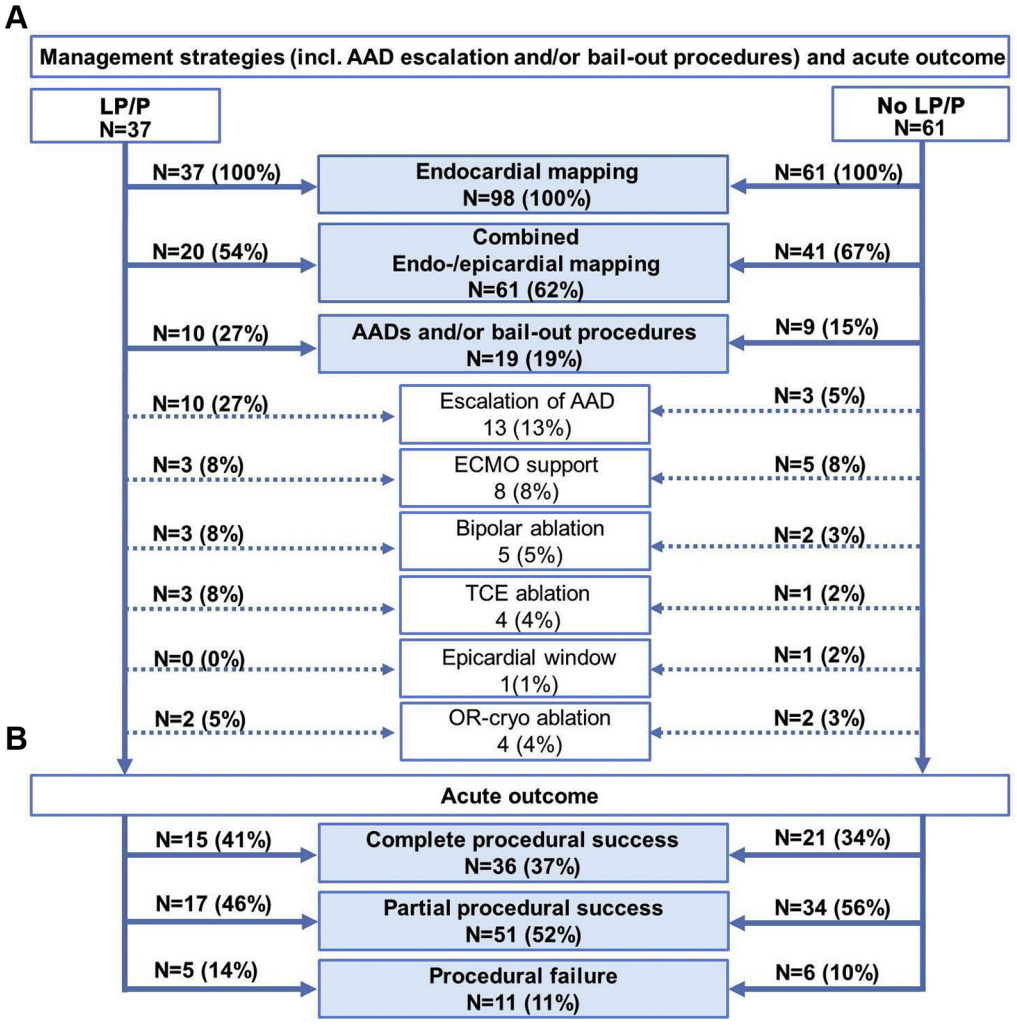
The locations of the VT substrates derived from EAVM are shown in the Central Illustration. Two distinct VT substrates were identified: a dominant basal AS in 48 (49%) patients and IL in 50 (51%) patients. Pericardial access for epicardial ablation was obtained in 61 (62%) patients: 22 of 61 (36%) with AS and 39 of 61 (64%) with IL substrates (p < 0.001). Among LP/P*v*+ patients, predominant substrates were located AS or IL in 22 (60%) and 15 (41%) patients, and among LP/P*v*- patients in 26 (43%) and 35 (57%) patients, respectively.

RELATIONSHIP BETWEEN SUBSTRATE LOCATION AND TYPE OF LP/P*V*. Figure 1 illustrates the dominant distribution of VT substrates across the LV regions for patients with distinct LP/P*v*. Of note, in patients with LP/P*v* in the *LMNA* and *TTN* genes, the basal AS segments were typically, yet not exclusively, involved. In contrast, patients with other LP/P*v* affecting the *PLN*, *SCN5A*, *DSP*, and *RBM20* genes showed a predominant IL involvement.

ACUTE OUTCOME. Figure 2 illustrates the different ablation strategies, including bailout interventional procedures and acute outcome data for both groups. Multiple procedures (≥2) were performed in 22 (22%) patients, and in 19 (19%) patients, bailout procedures or escalation of AADs were required to achieve arrhythmia control. The necessity of multiple and bailout procedures was not different between LP/P*v*+ and LP/P*v*- patients (9 [24%] vs. 13 [21%]; p = 0.70). Differences in the frequency of bailout procedures with regard to substrate location did not reach statistical significance (AS 11 [58%] vs. IL 8 [42%]; p = 0.40).

After the last procedure, there were no significant differences in acute ablation outcome between LP/P*v*+ and LP/P*v*- patients. Complete procedural success was achieved in 36 (37%), and partial success

FIGURE 2 Procedural Strategy and Alternative Procedures

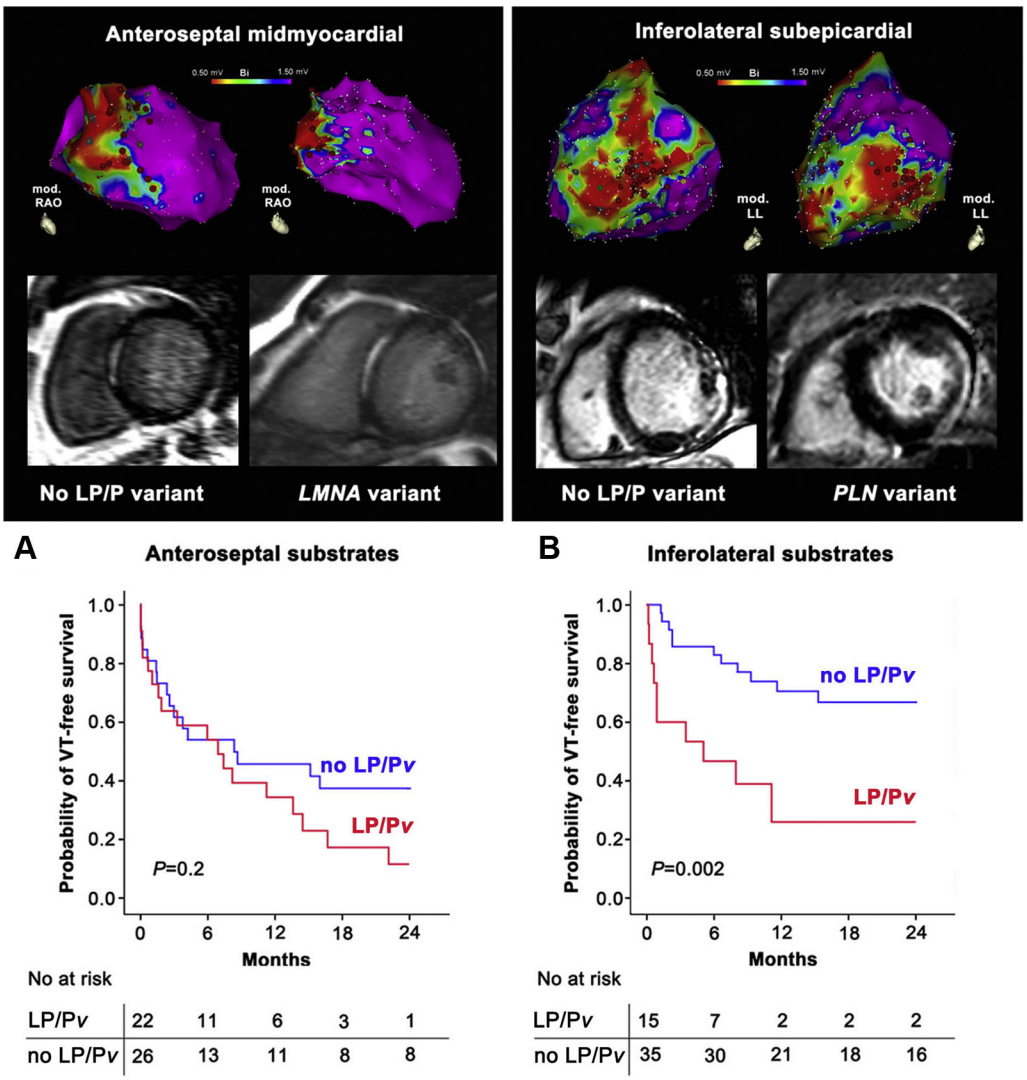


Procedural strategy and alternative procedures. AAD = antiarrhythmic drug; ECMO = extracorporeal membrane oxygenation; LP/P = likely pathogenic or pathogenic variants; OR = operating room; TCE = transcoronary ethanol.

was achieved in 51 (52%) patients. In the remaining 11 (11%) patients, the (presumed) clinical VT could not be abolished. Of note, in 4 of these 11 patients, no VT substrate could be identified precluding ablation. In the remaining 7 patients, ablation failure was attributed to the vicinity of coronary arteries, epicardial fat or conduction system (n = 4 of 7), or presence of a deep intramural septal substrate (n = 3 of 7). ICD therapy was offered to all 19 (47%) non-ICD carriers, of whom 9 received 1 after CA (LP/P*v*+ patients: n = 1 of 1 [100%] vs. LP/P*v*- patients: n = 10 of 18 [56%]). None of the remaining patients who refused to be discharged with an ICD experienced VT recurrence or died during follow-up.

LONG-TERM OUTCOME. The median follow-up after ablation was 28 months (IQR: 10 to 52 months) (LP/P*v*+ patients: 15 months [IQR: 5 to 45 months] vs. LP/P*v*- patients: 35 months [IQR: 15 to 59 months]; p = 0.05). During follow-up, 63 (64%) patients experienced VT recurrence after a median of 9 months (IQR: 2 to 28 months) (LP/P*v*+ patients: 6 months [IQR: 1 to 12 months] vs. LP/P*v*- patients: 12 months [IQR: 3 to 37 months]; p = 0.002). LP/P*v*+ patients had significantly higher VT recurrence rates than did LP/P*v*- patients (n = 30 of 37 [81%] vs. n = 33 of 61 [54%]; p = 0.007). Twenty-eight (29%) patients died (n = 24) or underwent HTx or LVAD implantation (n = 4) (LP/P*v*+ patients: n = 19 of 37 [51%] vs. LP/P*v*-

FIGURE 3 Different Types of Substrate Distributions and Related Outcomes



Cardiac magnetic resonance–derived scars of patients with or without likely pathogenic or pathogenic variants (LP/P) and corresponding bipolar electroanatomical voltage maps **(top)**. Kaplan-Meier estimates comparing 24-month VT-free survival according to the presence or absence of LP/P and dependent on the VT substrate location **(bottom)**. **(A)** Anteroseptal and **(B)** inferolateral epicardial substrates. LL = left lateral; RAO = right anterior oblique.

patients: n = 9 of 61 [15%]; p < 0.001). Cardiovascular death or HTx or LVAD (n = 20 [20%]) was also significantly more frequent among LP/P*v*+ patients (n = 14 of 37 [38%] vs. n = 6 of 61 [10%]; p = 0.001). The frequency of HTx or LVAD and different causes of death are shown in Supplemental Table 3.

Both the 24-month death or transplant-free survival (78% [95% confidence interval (CI): 69% to 87%]) and 24-month VT-free survival (41% [95% CI: 30% to 51%]) rates were significantly lower in LP/P*v*+ patients (61% [95% CI: 42% to 79%] and 16% [95% CI: 2% to 30%] vs. 88% [95% CI: 79% to 97%] and 54% [95% CI: 41% to 68%] in LP/P*v*- patients; p = 0.01 and p = 0.001, respectively) (**Central Illustration**). Concomitantly, the 24-month probability of VT recurrence (41% [95% CI: 30% to 52%]) was significantly higher among LP/P*v*+ patients (55% [95% CI: 41% to 68%] vs. 17% [95% CI: 2% to 31%] in LP/P*v*- patients; p = 0.001), as shown in the **Central Illustration**. **Figure 1B** illustrates the 24-month VT-free survival of patients with the 3 most frequent LP/P*v* (*LMNA*, *TTN*, and *PLN*) and the 24-month

VT-free survival of patients with *LMNA* variants versus non-*LMNA* variants (Figure 1C) compared with LP/P*v*- patients. Among LP/P*v*+ patients, the frequency of the combined endpoint VT recurrence or death at 24-month follow-up was high (*LMNA*: n = 11 of 11 [100%]; *TTN*: n = 6 of 6 [100%]; and *PLN*: n = 4 of 6 [67%]). Of interest, a subanalysis investigating patients' outcome according to substrate location showed a significantly lower 24-month VT-free survival of LP/P*v*+ patients versus LP/P*v*- patients, in particular for patients with IL substrates (Figure 3, lower panel).

PREDICTORS OF VT-FREE SURVIVAL AFTER CA. Table 3 depicts the results of univariate and multivariate Cox proportional hazards analysis to determine the association between baseline and procedural parameters and VT-free survival after 24 months. Presence of LP/P*v* (hazard ratio [HR]: 1.9; 95% CI: 1.1 to 3.4; p = 0.02) and a larger unipolar LVA (HR: 2.5 per cm^2 increase; 95% CI: 1.6 to 4.0; p < 0.001), were independently associated with a reduced 24-month VT-free survival.

TABLE 3 Univariate Cox Proportional Hazards Analysis of Baseline Covariates in Relation to Outcome Events (2-Year VT-Free Survival)

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age, per 10-yr increase	1.1	0.9-1.4	0.20	–	–	–
Male	1.2	0.6-2.4	0.60			
LVEF	1.0	0.9-1.0	0.02	–	–	–
Atrial fibrillation	1.5	0.9-2.6	0.10			
VT storm/incessant VT	1.2	0.7-2.2	0.40			
LP/P*v*	2.3	1.4-4.0	0.002	1.9	1.1-3.4	0.02
Anteroseptal substrate	2.1	1.2-3.6	0.008	–	–	–
Unipolar LVA (<8.01 mV), per cm^2 increase	2.9	1.8-4.5	<0.001	2.5	1.6-4.0	<0.001
Noncomplete procedural success	1.5	0.8-2.7	0.20			

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

DISCUSSION

MAIN FINDINGS. The present study is the first to evaluate the prevalence of LP/P*v* in patients with iDCM referred for ablation of MSVT. In addition, it is the first to study the impact of the presence of these variants on the VT substrate and acute and long-term ablation outcomes. The main results of the study can be summarized as follows: 1) LP/P*v* were identified in 38% of patients, despite a family history for DCM in only 15%; 2) after ablation, the 2-year VT-free survival of patients with LP/P*v* was significantly lower (16%) than in patients without (54%), independent of the substrate location; 3) the presence of LP/P*v* and the extension of unipolar LVA were independently associated with decreased 24-month VT-free survival; and 4) both cardiac and all-cause mortality were significantly higher in LP/P*v*+ patients.

HIGH PREVALENCE OF LP/P*V* AMONG DCM-VT PATIENTS. There is increasing evidence that genetic variants have an important role in the pathogenesis of DCM (15). Recent studies report a prevalence of ~20% of LP/P*v* among iDCM probands and between 25% and 50% with familial DCM (10,22,23). Of importance, DCM is classified as idiopathic when all detectable causes have been excluded with the exception of genetic causes as patients with genetic cardiomyopathy frequently present with idiopathic DCM. In addition, a large proportion of the significance of genetic variants remains unknown, and thus a negative genetic testing does not exclude an inherited disease. In our study, the prevalence of LP/P*v*+ patients with iDCM and MSVT was about twice (38%) as high as what has been reported for unselected DCM patients, despite the infrequent history of familial DCM (15%).

Not unexpectedly, LP/P*v* in the *LMNA* gene, which are known to be associated with MSVT, were the most prevalent (11%). Of interest, the second most frequent gene involved was *TTN*. Although disease-causing *TTN* variants can be identified in up to 30% in unselected DCM populations, they have been associated with a milder and, compared with laminopathies, less arrhythmogenic DCM (18,24). Data reporting an association of titinopathies with MSVT are limited. Recent data suggest that certain *TTN* variant carriers may be at high risk for increased myocardial fibrosis and life-threatening sustained VT or ventricular fibrillation (10). Our study extends these findings and is the first to show that various LP/P*v* including *TTN* can be associated with an iDCM, and specifically MSVT, with similarly poor outcomes after CA as described in patients with laminopathies (12).

ASSOCIATION BETWEEN UNDERLYING GENETIC DISEASE AND VT SUBSTRATE LOCATION. Prior studies have identified a dominant AS versus IL scar pattern as substrate for MSVT in DCM with a similar prevalence (6,21). Distinct LP/P*v* seemed to have a higher propensity for AS or IL substrates. In line with prior reports, patients with *LMNA* variants had more frequent, albeit not exclusive, AS substrates (12,25), which was also the dominant substrate location among *TTN* variant carriers. In contrast, patients with *DSP*, *RBM20*, and *PLN* had more often IL involvement, which is in line with recent CE-CMR and whole-heart histology data showing that desmosomal and *PLN* variants typically involve the outer posterolateral wall of the LV (26). Taken as a group,

LP/P*v*+ tended to have more AS substrates, mainly accessed from the endocardium, as epicardial mapping was anticipated (based on preprocedural imaging) to be hampered by anatomical obstacles such as coronary arteries, the left atrial appendage, or epicardial fat. In contrast, LP/P*v*- patients more often had inferolateral substrates, which were more frequently approachable from the epicardium. The higher frequency of AS substrates among LP/P*v*+ patients compared with LP/P*v*- patients may be explained by the relatively high proportion of *TTN* and *LMNA* variants.

POOR OUTCOMES AFTER CA IN INHERITED DCM. Reported VT recurrence rates and mortality after CA in unselected DCM patients range widely, from 29% to 77% and from 4% to 33%, respectively, during median follow-ups of 9 to 22 months. This may be also related to different distributions of substrate location and underlying etiologies across studies (2,3,27–29). VT recurrence rates have been shown to be significantly higher in patients with AS scars, which has been attributed to a deep intramural substrate extending toward the LV summit, which is difficult to reach by current ablation techniques (6,21). LP/P*v*+ patients in our study had a tendency to more AS substrates, which may contribute to the detrimental outcomes. Of interest, comparison of LP/P*v*+ versus LP/P*v*- patients within the 2 substrate types (AS vs. IL) showed that the prognosis after CA in LP/P*v*+ patients was particularly poor for IL substrates. Compared with AS substrates, IL substrates are usually better accessible due to a thinner overlying epicardial fat layer and the absence of major coronary branches precluding CA (21). In these patients, the presence of LP/LP*v* significantly determines outcome. In contrast, among patients with AS substrates ablation outcome is already poor, and the presence of LP/P*v* may have less impact. In this context, it is important to emphasize that, in particular IL, subepicardial substrates might be misclassified as post-myocarditis based on CE-CMR and EAVM, supporting the importance of genetics for long-term prognosis (26,30).

Arrhythmogenic iDCM has been proposed to be a manifestation of an early stage of the disease (5), and indeed, in our cohort 22% had an LVEF ≥50% and 64% had an LVEF ≥35%. Despite this large proportion of patients with only moderately reduced LVEF, outcomes were poor, in particular among LP/P*v*+ patients, of whom 49% had an LVEF ≥35%. Occurrence of MSVT may reflect a particular stage of the disease, in which a critical amount and perhaps a specific architecture of fibrosis provides the substrate for VT and may also lead to rapid progression to (end-stage) HF. The amount of fibrosis is reflected by lower unipolar LVA. The latter has been related to reduced wall thickness and a lower amount of viable myocardium (3,31,32). Of interest, multivariate analyses revealed that the extent of the unipolar LVA and the presence of a LP/P*v* were independently associated with a poor 2-year VT-free survival, suggesting that additional etiology related factors play a role.

GENETIC TESTING AS RISK-STRATIFICATION TOOL IN iDCM AND IMPLICATIONS FOR CLINICAL MANAGEMENT. The overall incidence of MSVTs in unselected DCM patients has been shown to be low, occurring in only 2% to 8% during a follow-up period of 6 to 68 months (33–35). Genetic screening of the small but highly important subgroup of iDCM with MSVTs may be of importance to identify those with a poor prognosis. This is particularly relevant for patients who do not meet current recommendations for genetic testing, such as progressive conduction disease, impaired LVEF or evidence for familial DCM (5,36). Although there may be a selection bias in our CA cohort, the majority of patients were off amiodarone (56%) and were referred after the first VT episode (54%). Familial cardiomyopathies are mostly inherited in an autosomal-dominant pattern. In addition to risk stratification of index patients, genetic testing may be helpful in identifying pre-symptomatic or affected relatives in whom life-threatening VTs may be the first disease manifestation (34). Furthermore, identification of an LP/P*v* allows for a tailored follow-up, screening for associated noncardiac disease manifestations, anticipatory therapeutic decisions including preventive ICD therapy, and when warranted, early treatment of arrhythmias and HF to control disease progression and on-time screening for HTx.

STUDY LIMITATIONS. We report on data from a single center with expertise in complex arrhythmia management, giving rise to a potential selection and referral bias toward more severely affected individuals. Additionally, patients were genetically tested consecutively since 2012, with missing data in 20 patients. Of note, because only DCM-VT survivors were tested, the number of affected individuals might be underestimated. Given the low incidence of iDCM presenting with MSVTs in general, the sample size of LP/P*v*+ patients is too small for further subgroup analysis.

CONCLUSIONS

Among iDCM patients with MSVTs, inherited cardiomyopathies represent a large proportion of

underlying etiologies. Management of inherited DCM patients with VTs is challenging due to high VT recurrence rates and increased mortality, which highlights the value of gene-based diagnosis. Incorporation of genetic testing in the comprehensive diagnostic work-up of patients with DCM-VTs may allow recognition of underdiagnosed inherited etiologies, which predict long-term outcomes after ablation and may enable initiation of family cascade screening and early anticipatory treatment.

ADDRESS FOR CORRESPONDENCE: Dr. Katja Zeppenfeld, Leiden University Medical Center, Department of Cardiology (C-05-P), P.O. Box 9600, 2300 RC Leiden, the Netherlands. E-mail: k.zeppenfeld@lumc.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with DCM and MSVT, a genetic cause is frequently found. Patients with (likely) pathogenic variants (LP/P*v*) have exceptionally high rates of VT recurrence and increased mortality. More extensive VT substrates in combination with disease progression may contribute to the poor prognosis. Therefore, patients presenting with DCM and MSVT should be systematically evaluated by genetic testing in order to identify a high-risk subgroup and affected (pre-symptomatic) relatives at risk.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify the mechanisms linking LP/P*v* to the (arrhythmogenic) clinical manifestations and differences of VT substrates.

REFERENCES

1. Briceno DF, Gupta T, Romero J, et al. Catheter ablation of ventricular tachycardia in nonischemic cardiomyopathy: A propensity score-matched analysis of in-hospital outcomes in the United States. J Cardiovasc Electrophysiol 2018;29:771–9.

2. Dinov B, Fiedler L, Schönbauer R, et al. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy: results from the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation 2014;129:728–36.

3. Muser D, Santangeli P, Castro SA, et al. Long-term outcome after catheter ablation of ventricular tachycardia in patients with nonischemic dilated cardiomyopathy. Circ Arrhythm Electrophysiol 2016;9:e004328.

4. Elliott P, Andersson B, Arbustini E, 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 2008;29:270–6.

5. Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J 2016;37:1850–8.

6. Oloriz T, Silberbauer J, Maccabelli G, et al. Catheter ablation of ventricular arrhythmia in nonischemic cardiomyopathy: anteroseptal versus inferolateral scar sub-types. Circ Arrhythm Electrophysiol 2014;7:414–23.

7. Gokoglan Y, Mohanty S, Gianni C, et al. Scar homogenization versus limited-substrate ablation in patients with nonischemic cardiomyopathy and ventricular tachycardia. J Am Coll Cardiol 2016;68:1990–8.

8. van den Hoogenhof MMG, Beqqali A, Amin AS, et al. RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. Circulation 2018;138:1330–42.

9. Begay RL, Graw SL, Sinagra G, et al. Filamin C truncation mutations are associated with arrhythmogenic dilated cardiomyopathy and changes in the cell-cell adhesion structures. J Am Coll Cardiol EP 2018;4:504–14.

10. Verdonschot JAJ, Hazebroek MR, Derks KWJ, et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J 2018;39:864–73.

11. Kumar S, Baldinger SH, Gandjbakhch E, et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. J Am Coll Cardiol 2016;68:2299–307.

12. Kumar S, Androulakis AF, Sellal JM, et al. Multicenter experience with catheter ablation for ventricular tachycardia in lamin A/C cardiomyopathy. Circ Arrhythm Electrophysiol 2016;9:e004357.

13. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies. Europace 2011;13:1077–109.

14. Hershberger RE, Givertz M, Ho CY, et al. Genetic evaluation of cardiomyopathy - a Heart Failure Society of America Practice Guideline. J Card Fail 2018;24:281–302.

15. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. Circ Res 2017;121:731–48.

16. Louis C, Calamaro E, Vinocur JM. Hereditary arrhythmias and cardiomyopathies: decision-making about genetic testing. Curr Opin Card 2018;33:78–86.

17. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72:1677–749.

18. McNally EM, Barefield DY, Puckelwartz MJ. The genetic landscape of cardiomyopathy and its role in heart failure. Cell Metab 2015;21:174–82.

19. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 2011;57:1641–9.

20. Piers SR, van Huls van Taxis CF, Tao Q, et al. Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischaemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging. Eur Heart J 2013;34:586–96.

21. Piers SRD, Tao Q, van Huls van Taxis CFB, Schalij MJ, van der Geest RJ, Zeppenfeld K. Contrast-enhanced MRI-derived scar patterns and associated ventricular tachycardias in nonischemic cardiomyopathy: implications for the ablation strategy. Circ Arrhythm Electrophysiol 2013;6:875–83.

22. van Spaendonck-Zwarts KY, van Rijsingen IA, van den Berg MP, et al. Genetic analysis in 418 index patients with idiopathic dilated cardiomyopathy: overview of 10 years' experience. Eur J Heart Fail 2013;15:628–36.

23. Ganesh SK, Arnett DK, Assimes TL, et al. Genetics and genomics for the prevention and treatment of cardiovascular disease: update: a scientific statement from the American Heart Association. Circulation 2013;128:2813–51.

24. Jansweijer JA, Nieuwhof K, Russo F, et al. Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. Eur J Heart Fail 2017;19:512–21.

25. Holmstrom M, Kivisto S, Helio T, et al. Late gadolinium enhanced cardiovascular magnetic resonance of lamin A/C gene mutation related

dilated cardiomyopathy. J Cardiovasc Magn Reson 2011;13:30.

26. Sepehrkhouy S, Gho J, van Es R, et al. Distinct fibrosis pattern in desmosomal and phospholamban mutation carriers in hereditary cardiomyopathies. Heart Rhythm 2017;14:1024–32.

27. Cano O, Hutchinson M, Lin D, et al. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. J Am Coll Cardiol 2009;54:799–808.

28. Wijnmaalen AP, Ebert M, Baldinger S, et al. The international, multicentre, dilated cardiomyopathy VT ablation registry (DCMVT): acute outcome and follow-up. Europace 2017;19:iii120.

29. Tung R, Vaseghi M, Frankel DS, et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: an International VT Ablation Center Collaborative Group study. Heart Rhythm 2015;12:1997–2007.

30. Te Rijdt WP, Ten Sande JN, Gorter TM, et al. Myocardial fibrosis as an early feature in phospholamban p.Arg14del mutation carriers: phenotypic insights from cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2019;20:92–100.

31. Glashan CA, Androulakis AFA, Tao Q, et al. Whole human heart histology to validate electroanatomical voltage mapping in patients with nonischaemic cardiomyopathy and ventricular tachycardia. Eur Heart J 2018;39:2867–75.

32. de Bakker JM, van Capelle FJ, Janse MJ, et al. Fractionated electrograms in dilated cardiomyopathy: origin and relation to abnormal conduction. J Am Coll Cardiol 1996;27:1071–8.

33. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30.

34. Losurdo P, Stolfo D, Merlo M, et al. Early arrhythmic events in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2016;2:535–43.

35. Zecchin M, Merlo M, Pivetta A, et al. How can optimization of medical treatment avoid unnecessary implantable cardioverter-defibrillator implantations in patients with idiopathic dilated cardiomyopathy presenting with "SCD-HeFT criteria?". Am J Cardiol 2012;109:729–35.

36. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015;17:1601–87.

KEY WORDS **catheter ablation, dilated cardiomyopathy, genetic mutation, genetic testing, genetic variant, inherited cardiomyopathy, nonischemic cardiomyopathy, ventricular tachycardia**

APPENDIX **For supplemental tables and a figure, please see the online version of this paper.**