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FOCUS ON VENTRICULAR ARRHYTHMIAS IN STRUCTURAL HEART DISEASE

Early Arrhythmic Events in Idiopathic Dilated Cardiomyopathy

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ABSTRACT

OBJECTIVES The study sought to provide an insight into the prevalence, characterization and possible reliable indicators of early sudden cardiac death/malignant ventricular arrhythmias (SCD/MVAs) in a large cohort of dilated cardiomyopathy (DCM).

BACKGROUND DCM generally affects young individuals and is characterized by an unpredictable prognosis with a non-negligible risk of SCD/MVAs, particularly in early stages of disease.

METHODS From 1988 to 2014, 952 patients with DCM were consecutively included in the Heart Muscle Disease Registry of Trieste.

RESULTS Globally, 20 patients (2.1% of the overall population) experienced SCD/MVAs within the first 6 months after enrollment (primary endpoint). At baseline they showed a worse functional class (New York Heart Association functional class III to IV 42% vs. 22%, $p = 0.038$), a longer QRS complex duration (127 ± 41 ms vs. 108 ± 33 ms; $p = 0.013$) and a larger indexed left ventricular end-systolic volume (LVESVI) (82 ± 49 ml/m^2 vs. 67 ± 34 ml/m^2; $p = 0.049$), as compared to patients without early SCD/MVAs. Beta-blockers were less tolerated (59% vs. 83% in patients with no early SCD/MVAs; $p = 0.008$), mostly due to hemodynamic intolerance. At multivariate analysis, LVESVI (odds ratio [OR]: 1.012; 95% confidence interval [CI]: 1.000 to 1.024; $p = 0.043$) and QRS complex duration (OR: 1.017; 95% CI: 1.003 to 1.030; $p = 0.015$) were independently associated with the primary endpoint, whereas beta-blockers demonstrated a protective effect (OR: 0.169, CI: 0.048 to 0.593; $p = 0.006$).

CONCLUSIONS Patients with DCM present a significant risk of major arrhythmic events in the first phase of the disease. Baseline LVESVI, QRS duration, and intolerance to beta-blocker therapy might be useful tools in the arrhythmic early risk assessment. (J Am Coll Cardiol EP 2016;2:535–43) © 2016 by the American College of Cardiology Foundation.

Dilated cardiomyopathy (DCM) is a heterogeneous myocardial disease with a variable clinical presentation and evolution, generally affecting young individuals (1). After therapy initiation DCM patients frequently recover left ventricular (LV) function with a subsequent favorable outcome (1). Unfortunately some major cardiac events may occur early after diagnosis. Risk stratification of sudden cardiac death (SCD) and malignant ventricular arrhythmias (MVAs) in the early phases

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ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

DHF/HTx = heart failure death or urgent heart transplantation

HF = heart failure

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVEF = left ventricular ejection fraction

LVESVI = indexed left ventricular end-systolic volume

MVA = major ventricular arrhythmia

OR = odds ratio

NYHA = New York Heart Association

SCD = sudden cardiac death

WCD = wearable cardioverter-defibrillator

of the disease remains challenging in the clinical management of DCM. Primary prevention implantable cardioverter-defibrillator (ICD) insertion indeed is currently recommended only for persisting high-risk patients (New York Heart Association [NYHA] functional class II to III and left ventricular ejection fraction [LVEF] ≤35%) after an adequate period of optimal medical therapy (2), whereas the characterization of DCM patients at risk for early life-threatening arrhythmias during the optimization of medical therapy is limited and no large-scale studies examined predictors of early SCD/MVA.

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Therefore, we sought to: 1) describe the characteristics and the prevalence of DCM patients with early (i.e., <6 months after enrollment) SCD/MVAs; and 2) identify possible baseline indicators of early major arrhythmic events to improve the arrhythmic risk stratification in the first phase of the disease.

METHODS

STUDY POPULATION. We retrospectively analyzed 952 DCM patients consecutively enrolled in the Heart Muscle Disease Registry of Trieste from 1988 to 2014. The diagnosis of DCM was determined according to the currently accepted criteria (3). Enrolled patients presented LVEF <50% at baseline evaluation in the absence of any possible cause of systolic impairment: significant coronary artery disease (stenosis >50% of a major coronary artery) was ruled out by coronary angiography in each patient; patients with a history of severe systemic hypertension (>160/100 mm Hg), alcohol intake over 100 g/day, severe organic valve diseases, congenital heart diseases, and advanced systemic disease affecting short-term prognosis were excluded. Persistent high-rate supraventricular arrhythmias were considered exclusion criteria if documented in the 6 months before enrollment, but patients with impaired LVEF 6 months after the resolution of the arrhythmia were included (4). Until 1992, all patients underwent endomyocardial biopsy to exclude active myocarditis according to the "Dallas Criteria." Thereafter, biopsy was performed on patients with recent onset heart failure refractory to conventional therapy, severe LV systolic dysfunction, and/or unexplained life-threatening ventricular arrhythmias (5). Patients with biopsy-proven active myocarditis were excluded, whereas patients with previous, healed myocarditis and persistent LV systolic dysfunction 1 year after diagnosis were enrolled in the Registry and included in the analysis. Patients with a history of SCD/MVAs and/or ICD implantation for secondary prevention at the time of the first evaluation at our center have been excluded from the present analysis by protocol.

All patients underwent a complete clinical and laboratory evaluation at baseline and at follow-up, including blood tests, 12-lead electrocardiography, 24-h Holter monitoring, and a complete transthoracic echocardiography. The familial history was strictly investigated and all familial DCM cases fulfilled the published criteria (6).

After enrollment, if not contraindicated, all patients received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blocker treatment titrated to the higher tolerated dose. Daily dosages of angiotensin-converting enzyme inhibitors and beta-blockers are reported as equivalents of enalapril and carvedilol, respectively (7), and refer to the end of titration period (generally 1 to 3 months after enrollment).

Decisions regarding ICD implantation for primary prevention were made by the managing cardiovascular specialists in selected patients with DCM considered at high risk for SCD (i.e., persistent LV dysfunction with LVEF ≤35% and NYHA functional class II to III classes on chronic optimal medical treatment) (2). Antitachycardia pacing (at least 2 bursts) followed by multiple shocks (5 to 8) was programmed for the treatment of arrhythmias recognized as ventricular tachycardias ranging between 185 and 220 to 230 beats/min, whereas tachyarrhythmias faster than 220 to 230 beats/min were treated with multiple shocks (on antitachycardia pacing before or during capacitor charging according to device facilities). Arrhythmic events were evaluated during routine or urgent evaluations at the ICD outpatient clinic by an expert electrophysiologist.

The institutional ethical board approved the study and the informed consent was obtained under the institutional review board policies of hospital administration. Information regarding the endpoints was obtained from the patients, their physician or the registers of death of the municipalities of residence.

ECHOCARDIOGRAPHIC ANALYSIS. LV dimensions as well as systolic and diastolic function were assessed according to international guidelines (8). Specifically, LV volumes and LVEF were calculated by Simpson's biplane method, left atrial size was assessed by end-systolic left atrial area. All volumes and areas were indexed according to body surface area.

Functional mitral regurgitation was assessed using a multiparametric approach following current recommendations (9). All measurements were obtained from the mean of 3 beats (patients in sinus rhythm) or 5 beats (atrial fibrillation).

STUDY DESIGN. The primary endpoint was a composite of SCD and MVA (defined as aborted SCD, sustained ventricular tachycardia, appropriate ICD shocks on syncope or >200 beats/min ventricular tachycardia) within the first 6 months after enrollment. SCD was defined as immediate death or death occurring within 1 h after the onset of symptoms, or during sleep in stable NYHA functional class I to III patients (10). Sustained ventricular tachycardia was defined in presence of duration of at least 30 s or development of hemodynamic compromise. Heart failure (HF) death or urgent heart transplantation (DHF/HTx) were also recorded and patients that experienced DHF/HTx in the first 6 months were then analyzed separately. Follow-up ended at the date of primary endpoint or DHF/HTx in the first 6 months and at the sixth month after enrollment for the remaining patients.

STATISTICAL ANALYSIS. Summary statistics of clinical and instrumental variables at enrollment were expressed as mean ± SD, or median (interquartile range), or counts and percentage, as appropriate. Comparisons between groups were made by an analysis of variance on continuous variables, using the robust Brown-Forsythe test when appropriate. The chi-square test was calculated for discrete variables using the Fisher exact test when necessary. Markers predictive of SCD/MVAs were searched by means of univariable logistic regression models, testing all clinical and instrumental variables measured at enrollment. Then a multivariable logistic regression model for SCD/MVAs was estimated, entering the list of statistically significant and clinically relevant parameters at the univariable analysis, and we reported only the subset of significant ones at the multivariable modeling selected by means of a backward-conditional stepwise algorithm. An internal validation procedure using a bootstrap technique was done in order to evaluate the amount of overfitting (11) and the results were satisfactory (the internal validation procedure showed that the amount of overfitting was negligible: the randomization estimate of optimism was 0.04 and estimated shrinkage was 0.09 (if optimism is absent, shrinkage factor is equal to 1). To verify the robustness of the variable selection procedure, we estimated also a penalized multivariable logistic regression model, starting from the full initial list of potential predictors, by using the R library "logistf" (12). Results were regarded as statistically significant when $p < 0.05$. All calculations were performed using IBM SPSS 19.0 (SPSS Inc., Chicago, Illinois) and the R package 3.10 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Characteristics of the Study Population According to the Primary Endpoint and DHF/HTx

	Total (n = 952)	MVAs (n = 20)	No-MVAs (n = 919)	p Value	DHF/HTx (n = 13)
Age (yrs)	46 ± 14	48 ± 19	45 ± 14	0.561	28 ± 16
Male (%)	70	80	70	0.331	77
Time from diagnosis to study enrollment (months)	1 [0.0-7.0]	2 [0.0-12.0]	1 [0.0-7.0]	0.845	1 [0.0-7.0]
Familial history of SCD (%)	10	14	11	0.697	8
Familial DCM (%)	21	14	24	0.413	8
History of syncope (%)	5	4	15	0.090	0
NYHA functional class I (%)	36	35	37	0.838	0
NYHA functional class III-IV (%)*	23	42	22	0.038	69
SBP (mm Hg)	124 ± 18	125 ± 19	124 ± 17	0.907	107 ± 14
GFR (ml/min)	93 ± 31	93 ± 26	93 ± 31	0.934	89 ± 21
Sinus rhythm (%)	84	88	90	0.863	85
LBBB (%)	29	37	31	0.576	8
QRS complex duration (ms)*	108 ± 33	127 ± 41	108 ± 33	0.013	89 ± 37
QTc (ms)	433 ± 56	451 ± 39	434 ± 57	0.550	426 ± 39
LVEDDI (mm/m^2)	36 ± 20	36 ± 6	37 ± 16	0.985	42 ± 7
LAAI (cm^2/m^2)	14 ± 0.2	14 ± 1	14 ± 0.2	0.824	19 ± 1
LVEDVI (ml/m^2)	97 ± 38	109 ± 50	96 ± 37	0.150	134 ± 40
LVESVI (ml/m^2)*	68 ± 35	82 ± 49	67 ± 34	0.049	103 ± 34
LVEF (%)	33 ± 13	29 ± 14	33 ± 13	0.130	23 ± 7
LVEF ≤35%	60	56	60	0.741	92
Shortening fraction RV (%)	18 ± 11	16 ± 8	19 ± 11	0.418	11 ± 3
Moderate-severe MR (%)	33	35	33	0.832	77
RFP (%)	20	28	27	0.954	77
VEB >5,000/day (%)	12	15	17	0.853	15
nsVT (%)	29	39	50	0.430	46
nsVT >5/day (%)	8	23	13	0.280	8
ICD implantation	4	5	4	0.570	7
ACEi/ARBs (%)	93	100	93	0.248	100
Enalapril equivalent dosage (mg/day)	20 ± 12	17 ± 11	20 ± 12	0.526	15 ± 9
Beta-blockers (%)*	79	59	83	0.008	77
Carvedilol equivalent dosage (mg/day)	40 ± 26	41 ± 49	40 ± 26	0.990	23 ± 30
Digitalis (%)	52	77	54	0.069	92
Diuretics (%)	61	71	63	0.527	100
MRAs (%)	14	3	14	0.923	3

Values are mean ± SD, %, or median [interquartile range]. *Statistically significant difference between MVAs and no-MVAs groups.

ACEi/ARB = angiotensin-converting inhibitor/angiotensin receptor blocker; DBP = diastolic blood pressure; DHF/HTx = HF death/heart transplantation; GFR = glomerular filtration rate; HF = heart failure; HR: heart rate; ICD = implantable cardioverter-defibrillator; LAAI = indexed left atrium area; LBBB = left bundle branch block; LVEDDI = indexed left ventricular end-diastolic diameter; LVEDVI = indexed left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESVI = indexed left ventricular end-systolic volume; MR = mitral regurgitation; MRA = mineralocorticoid-receptors-antagonist; MVA = major ventricular arrhythmias; nsVT = ventricular tachycardia; RBBB = right bundle branch block; RFP = restrictive filling pattern; RV = right ventricle; SBP = systolic blood pressure; VEB = ventricular ectopic beats.

RESULTS

CHARACTERIZATION OF PATIENTS WITH EARLY SCD/MVAs. Table 1 (first column) shows the baseline

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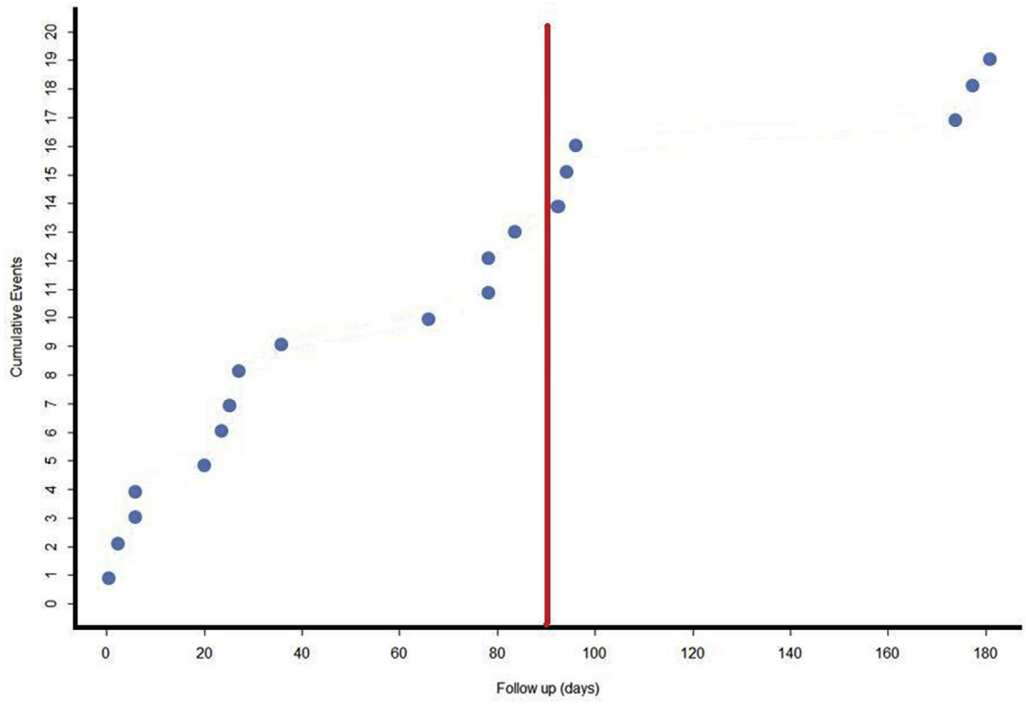
FIGURE 1 Scatter Plot of Sudden Cardiac Death/Major Ventricular Arrhythmias (Cumulative Events) During the First 6 Months After Enrollment



The time distribution of the primary outcome showed that 70% of early sudden cardiac death/major ventricular arrhythmias occurred within the first 90 days **(red line)**.

characteristics of the 952 enrolled patients (46 ± 14 years of age, 70% male). They were characterized by a short duration of symptoms (median time from diagnosis to study enrollment 1 month; interquartile range: 0 to 7 months; mean 9 ± 22 months). Familial forms of DCM accounted for 21% of the overall population, whereas 10% had a family history of SCD. Globally, 36% of patients were asymptomatic (NYHA functional class I) at enrollment, 29% had left bundle branch block, 20% had LV restrictive filling pattern, and the mean LVEF was 33 ± 13%. Concerning medical treatment, only 16% and 45% of patients were treated with beta-blockers and angiotensin-converting enzyme inhibitors, respectively, at the time of referral, mostly at suboptimal dosages. After enrollment, 93% of patients received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and 79% beta-blockers, titrated to the higher tolerated dose (20 ± 12 mg/day of enalapril equivalent dosage, and 40 ± 26 mg/day of carvedilol equivalent dosage).

The primary endpoint occurred in 20 patients (2.1% of the overall population): 13 SCD, 7 MVA. Of note, 14 of the 20 primary events (70%) occurred within the first 90 days from inclusion (Figure 1). The baseline characteristics of patients experiencing primary endpoint, compared to patients without early major cardiovascular events (919 cases), are reported in Table 1 (second and third columns). The 2 subgroups were mostly similar, although patients with SCD/MVAs presented a more advanced functional class (NYHA functional class III to IV 42% vs. 22%; $p = 0.038$), a longer QRS complex duration (127 ± 41 ms vs. 108 ± 33 ms; $p = 0.013$) and a larger LVESVI (82 ± 49 ml/m^2 vs. 67 ± 34 ml/m^2; $p = 0.049$) in patients with early SCD/MVAs. In addition, fewer patients with early SCD/MVA were treated with beta-blockers (59% vs. 83%; $p = 0.008$), due to hemodynamic intolerance (80%) or significant sinus bradycardia (20%). During the study period, few patients in both groups received an ICD for primary prevention (4% vs. 5%; $p = 0.57$), and no patients experienced ICD shocks.

Finally, as specified previously, patients that experienced DHF/HTx in the first 6 months ($n = 13$, 1.3%) were excluded and then analyzed separately (Table 1). Compared to the others, these patients were younger, with a more severe HF (NYHA functional

class III to IV in 69% of cases) and a significantly remodeled LV (indexed left ventricular end-diastolic diameter 42 ± 7 mm/m^2, indexed left ventricular end-diastolic volume 134 ± 40 ml/m^2, LVEF 23 ± 7%) at the time of enrollment.

EARLY PARAMETERS ASSOCIATED WITH EARLY MALIGNANT ARRHYTHMIC EVENTS. A multivariable analysis (Table 2) was performed on the basis of the variables significantly associated with SCD/MVAs at univariable analysis (Table 2). QRS complex duration (odds ratio [OR] for 1 ms increase: 1.017; 95% confidence interval [CI]: 1.003 to 1.030; p = 0.015) and LVESVI (OR for 1 ml/m^2 increase: 1.012; 95% CI: 1.000 to 1.024; p = 0.043) emerged as independently associated with SCD/MVAs. Moreover, beta-blocker therapy demonstrated a protective effect (OR: 0.169; CI: 0.048 to 0.593; p = 0.006) toward the primary endpoint. The internal validation procedure showed that the amount of overfitting was negligible: the randomization estimate of optimism was 0.04 and estimated shrinkage was 0.09 (if optimism is absent, shrinkage factor is equal to 1). Finally, the combination of these parameters showed a good accuracy at the ROC analysis (area under the curve: 0.76; 95% CI: 0.67 to 0.89) (Figure 2). A linear correlation with the study endpoint was found for both LVESVI and QRS complex duration, therefore definite cutpoints for the 2 variables were not detectable (Figure 3).

Interestingly, baseline severe LV dysfunction was not predictive of early SCD/MVAs (OR: 0.363; 95% CI: 0.09 to 1.30; p = 0.147). Among the 507 patients (55% of the overall population) with LVEF ≤35%, 47% improved LVEF over 35% at 6-month follow-up (interquartile range: 3 to 9 months). A supplementary analysis has been performed to test the ability of the 2 continuous variables independently associated with the study endpoint (i.e., LVESVI and QRS complex duration) to predict the probability of LVEF improvement. An inverse linear relation has been found for both the parameters. Thus, for every unit increase in LVESVI (OR: 1.027; 95% CI: 1.016 to 1.038; p < 0.001) and QRS complex duration (OR: 1.013; 95% CI: 1.004 to 1.022; p = 0.006), the likelihood of LV function improvement at 6 months progressively decreases.

To rule out the possible influence of the enrollment period on the primary endpoint, the decade of enrollment and presence of symptoms (NYHA functional class I+) have been additionally tested. The decade of enrollment had borderline significant relation at univariate analysis (p = 0.071), not confirmed at the multivariable analysis (p = 0.165). Even presence of symptoms (NYHA functional class I+) was not associated with an increased risk of early major events.

TABLE 2 Univariate and Multivariate Independent Predictors of SCD/MVAs

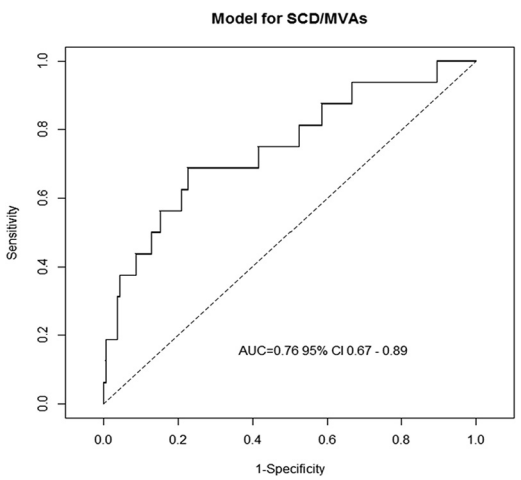
	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
History of syncope	3.300	1.1–14.0	0.035			
Year of enrolment 1987-1997 vs. ≥1998	2.300	0.9–5.7	0.071			
NYHA functional class I	0.865	0.400–2.195	0.721			
NYHA functional class III-IV	2.343	0.945–5.800	0.066			
LVESVI*	1.010	0.999–1.021	0.043	1.012	1.000–1.024	0.043
LVEF*	0.965	0.923–1.008	0.109			
LVEF ≤35%	0.853	0.333–2.185	0.741			
QRS complex duration*	1.015	1.003–1.026	0.011	1.017	1.003–0.030	0.015
Beta-blockers	0.285	0.107–0.762	0.012	0.169	0.048–0.593	0.006

*For every unit increase.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

DISCUSSION

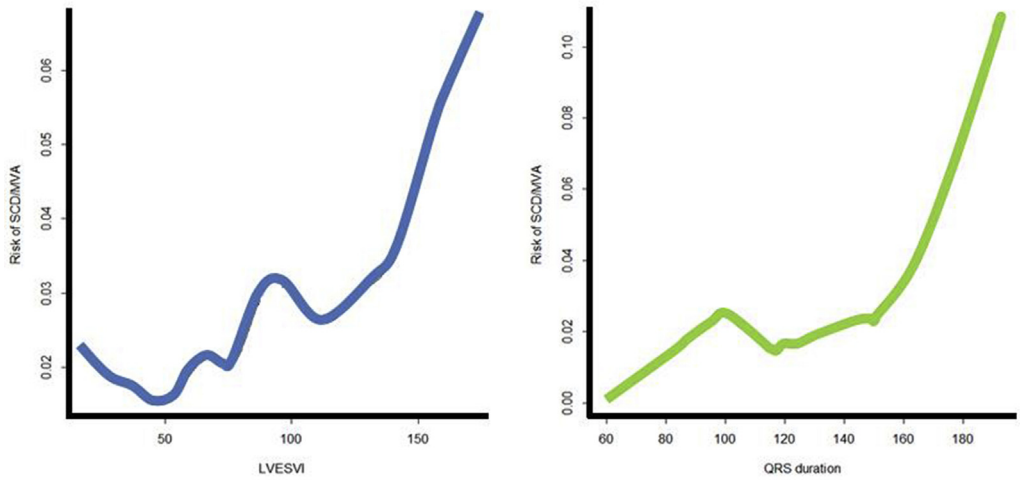
The main findings of the present study are: 1) about 2% of a large population of DCM patients enrolled with homogeneous criteria at the same institution experienced SCD/MVAs early after diagnosis, during the optimization of medical treatment; 2) larger LVESVI and QRS complex duration at baseline, as expression of a less favorable presentation or a more

FIGURE 2 Receiver-Operating Characteristic Curve for the Primary Endpoint (Early SCD/MVAs)



Predictive accuracy of the model including indexed left ventricular end-systolic volume, QRS duration and beta-blocker therapy. AUC = area under the curve; CI = confidence interval; SCD/MVAs = sudden cardiac death/major ventricular arrhythmias.

FIGURE 3 Observed Risk of Sudden Cardiac Death/Major Ventricular Arrhythmia



Observed risk of sudden cardiac death/major ventricular arrhythmia (SCD/MVA) on the basis of indexed left ventricular end-systolic volume (LVESVI) **(blue line)** and QRS duration values **(green line)**.

advanced disease, emerged as independently associated with early SCD/MVAs; and, finally, 3) DCM patients not tolerating beta-blocker therapy are exposed to an increased risk of early SCD/MVAs since the time of diagnosis.

To our knowledge, this is the largest available case series of DCM patients specifically evaluated for the incidence of major arrhythmic events in the first phase of the disease. Our findings might be helpful to identify patients at the higher arrhythmic risk who might benefit from early preventive measures including a wearable cardioverter-defibrillator (WCD), regardless of the optimization of medical therapy.

PREVALENCE OF EARLY SCD/MVA IN DCM. Patients with DCM are classically younger, with fewer comorbidities and a lower expected mortality for noncardiac causes compared to other etiologies of systolic HF, reinforcing the importance of solid strategies to reduce arrhythmic events (13). The large improvement in SCD free survival (98% at 8 years) in patients diagnosed in the last decades attested the favorable impact of the current evidence-based strategies. Interestingly, arrhythmic events occurred mainly in the first phase of the disease (4). Similarly, the IMAC2 (Intervention in Myocarditis and Acute Cardiomyopathy-2) study, including recently onset DCMs, reported a 1- and 2-year SCD rate of 1% and 2%, respectively (14). Consistently, in the present study, 2.1% of patients died by SCD or experienced MVAs in the first 6 months after diagnosis, regardless of the enrollment period.

CHARACTERIZATION AND PROGNOSTIC ASSESSMENT OF EARLY SCD/MVA. Evidences supporting ICD implantation in DCM are less definitive than in ischemic patients. The 2 largest trials that showed a decrease in arrhythmia-related events for ICD strategy in DCM yielded only a nonsignificant reduction in overall mortality, raising the main issue of the correct selection of high-risk subgroups who could mainly benefit from ICD (15,16).

Currently, the recommendations addressing ICD strategy for primary prevention of SCD are only on the basis of LV function and symptoms (i.e., LVEF ≤35% and NYHA functional class II to III) (2). However, in newly diagnosed DCM, a significant proportion of patients presenting with severely depressed LVEF shows an improvement after starting medical therapy, increasing the controversy with respect to the optimal timing of device implantation. In the IMAC2 study cohort (14) early ICD strategies did not impact on survival. Kadish et al. (17) reported a benefit from ICD in nonischemic patients more recently diagnosed (<3 months) that was at least as prominent as in patients with remote disease, attesting once again the weakness of the current selection criteria. Current evidences suggest deferring ICD implantation for a period after medical therapy optimization, but no literature data exists on the progressive risk of delay. Therefore, several aspects still need to be addressed to move forward in the identification of the best candidates for primary prevention of SCD: the optimal timing for ICD implantation; the identification of

additional parameters others than LVEF, improving risk stratification particularly in earlier stages; the identification of nonresponders to medical therapy, hence potentially suitable for early ICD implantation.

In our study, most of the early events occurred within the third month after enrollment and no interventions were observed in ICD carriers, confirming the need of future efforts at improving early arrhythmic risk evaluation (**Figure 1**). Moreover, LVEF was not predictive of SCD/MVAs in the first phase of disease.

Despite a large number of available and potentially promising techniques that have been proposed to improve the SCD/MVAs risk stratification in DCM, the real addictive role played in the discrimination of patients eligible for early ICD implantation remains unclear (18). There is growing evidence that the presence and extent of late gadolinium enhancement on cardiac magnetic resonance could provide a convincing additional value for arrhythmic risk assessment. Nevertheless, most of the studies performed their analysis across a longer follow-up (19), whereas the role of cardiac magnetic resonance in supporting the selection of early candidates for ICD has not been tested.

We found that 2 easily and rapidly accessible parameters evaluated at the time of referral, such as QRS duration at electrocardiography and LVESVI were associated with an increased likelihood of SCD/MVA in the first 6 months, independently from LVEF. These findings might implement the early arrhythmic stratification of DCM patients. There was a linear risk correlation for both the variables, thus it has not been possible to identify a cutpoint clearly discriminating patients at higher risk. However this is beyond the aims of the present study and needs to be evaluated in future prospective series.

Former studies correlated the QRS duration with a higher rate of SCD both in general and in chronic HF populations. In the subgroup analysis of the SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial), patients with a QRS duration ≥120 ms had a larger benefit from ICD therapy (16). Hombach et al. (20) showed that QRS duration yielded a strong risk of adverse outcome also in DCM. Nevertheless, in the survival curves the prognosis diverged in the late follow-up. Conversely, our data strengthened its importance yet in the first period of the disease. It is likely that a large QRS complex at presentation might be the marker of a more advanced and structured disease.

Similarly, a more dilated LV can be the result of a long-standing disease despite the short duration of overt HF symptoms and the low functional class characterizing our high-risk cohort at baseline. Especially for young patients, the distinction between truly recent DCM, with higher probability of improvement after treatment initiation, and previously unrecognized chronic diseases typically yielding a lower rate of improvement and an increased arrhythmic risk, is extremely challenging. LVESVI has been previously associated with a lower rate of LV function recovery (21), whereas former data failed to demonstrate the relationship between LVESVI and arrhythmic events in patients with HF by different etiologies (21). In the present study LVESVI emerged for the first time as an independent predictor of short-term MVA in recent onset DCM. Moreover, it was also inversely related with the probability of LVEF improvement over 35% at 6-month follow-up, along with QRS duration. This issue might further reinforce the potential of these 2 variables into the assessment of early arrhythmic risk of DCM patients, leading to consider strategies for primary SCD prevention.

As an alternative to conventional approaches, WCD clearly demonstrated safety and effectiveness in a 2,000-patient registry, with very high compliance and minimal rate of inappropriate shocks. Although 64% of nonischemic patients did not require ICD implantation after 3 months as LVEF improved, WCD drove the decision making in patients experiencing life-threatening arrhythmias while wearing the device (22). Therefore, in newly diagnosed DCM presenting with similar risk indicators of increased early arrhythmic risk, WCD can be considered in the initial phase of therapeutic optimization.

Finally, the protective effect of beta-blocker therapy toward SCD has been widely demonstrated and the lack of its administration was predictive of MVAs in a previous study in nonischemic patients. Importantly, in our population who did not tolerate beta-blockers since the time of enrollment carried a higher rate of events already in the first period after diagnosis, suggesting a very poor myocardial substrate. Thus, the inability to start the optimal therapy on the basis of beta-blockers lays soon these patients in a higher risk class for SCD/MVAs.

STUDY LIMITATIONS. Several limitations need to be acknowledged. As do all observational studies on long-term registries, it suffers from the common bias of different selection criteria, protocols, and treatments. Furthermore, the relatively small number of events might underestimate the role of some potential predictors and the proposed multivariable model should be validated in larger series.

As the inclusion period started in 1988, all the latest therapy such as antialdosterone drugs and ivabradine were not widely administrated. However, this allowed us to analyze a larger study population of

DCM patients, compared with other published series, appropriate to focus the attention on subgroups otherwise poorly represented, especially in clinical trials. Furthermore, the enrollment period was not independently associated with the study endpoint at multivariate analysis.

Patients that underwent ICD implantation in the first 6 months were not excluded by the analysis. ICD interventions were analyzed during routine evaluation by the outpatient ICD clinic and an expert electrophysiologist; therefore, as no blinded review of the records was performed, false positive and negative, though unlikely, cannot be excluded. However, no patients experienced ICD interventions during the study period.

Another potential bias concerns the arbitrary chosen timing of early events. The eligibility for ICD implantations should be deferred at least 3 months after the optimization of medical therapy, but to date the optimal time delay after therapy initiation has not been universally defined, particularly in DCM setting. According to evidences from major clinical trials, in our Institution patients are systematically reassessed 6 months after the optimization of medical treatment, also in view of possible invasive strategies (i.e., ICD or cardiac resynchronization therapy implantation) (15,18).

Furthermore, few patients were already on evidence-based therapy before the first contact at our Center and the starting dosage was not always available, though rarely on target. However, the whole population had a relatively recent documented onset of the disease, as indicated by the short duration of symptoms before the first evaluation (median 1 month). Removing patients referred from other centers could lower the statistical power of the analysis due to the rarity of early arrhythmic events in this heart muscle disease. Afterward, all patients without contraindications started the recommended treatment at maximum tolerated dose since the first evaluation.

Cardiac magnetic resonance (routinely performed in our center since 2011), B-type natriuretic peptide values, data from electrophysiology study, long-term Holter monitoring, heart rate variability, T-wave alternans and genetic data were not systematically available and should be assessed in future dedicated prospective investigation. Autopsy was not regularly performed in patients died suddenly, thus post-mortem data were not available.

CONCLUSIONS

DCM carries a not-negligible risk of SCD/MVAs already in the early phase of the disease. In this study we provided important insights into the arrhythmic early risk assessment of DCM patients. Simple and easily accessible parameters such as QRS duration and LVESVI emerged as promising tools for the risk characterization. Furthermore, the large impact of beta-blockers emphasizes once again the key and fundamental role of optimal medical therapy. Future multicenter studies, possibly incorporating the more recent and promising techniques for risk assessment, are needed to confirm these results and to further improve the early stratification of these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: DCM is characterized by a significant risk of life-threatening arrhythmias even in the early stages, during optimization of medical treatment. QRS duration and left ventricular end-systolic volume are simple but powerful tools in the early risk assessment.

TRANSLATIONAL OUTLOOK: Early preventive measures including WCD for patients at risk should be explored in randomized clinical studies and selection criteria should incorporate additional markers of risk other than conventional evaluation of left ventricular function.

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