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Incidence of and Risk Factors for Sudden Cardiac Death in Children With Dilated Cardiomyopathy

A Report From the Pediatric Cardiomyopathy Registry

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Objectives The purpose of this study was to establish the incidence of and risk factors for sudden cardiac death (SCD) in pediatric dilated cardiomyopathy (DCM).

Background The incidence of SCD in children with DCM is unknown. The ability to predict patients at high risk of SCD will help to define who may benefit most from implantable cardioverter-defibrillators.

Methods The cohort was 1,803 children in the PCMR (Pediatric Cardiomyopathy Registry) with a diagnosis of DCM from 1990 to 2009. Cumulative incidence competing-risks event rates were estimated. We achieved risk stratification using Classification and Regression Tree methodology.

Results The 5-year incidence rates were 29% for heart transplantation, 12.1% non-SCD, 4.0% death from unknown cause, and 2.4% for SCD. Of 280 deaths, 35 were SCD, and the cause was unknown for 56. The 5-year incidence rate for SCD incorporating a subset of the unknown deaths is 3%. Patients receiving antiarrhythmic medication were at higher risk of SCD (hazard ratio: 3.0, 95% confidence interval: 1.1 to 8.3, $p = 0.025$). A risk stratification model based on most recent echocardiographic values had 86% sensitivity and 57% specificity. Thirty of 35 SCDs occurred in patients who met all these criteria: left ventricular (LV) end-systolic dimension *z*-score >2.6, age at diagnosis younger than 14.3 years, and the LV posterior wall thickness to end-diastolic dimension ratio <0.14. Sex, ethnicity, cause of DCM, and family history were not associated with SCD.

Conclusions The 5-year incidence rate of SCD in children with DCM is 3%. A risk stratification rule (86% sensitivity) included age at diagnosis younger than 14.3 years, LV dilation, and LV posterior wall thinning. Patients who consistently meet these criteria should be considered for implantable cardioverter-defibrillator placement. (Pediatric Cardiomyopathy Registry; NCT00005391) (J Am Coll Cardiol 2012;59:607–15) © 2012 by the American College of Cardiology Foundation

In adults, sudden cardiac death (SCD) accounts for substantial mortality in nonischemic cardiomyopathy, with deaths from congestive heart failure (CHF) and SCD occurring in nearly equal numbers (1). Large randomized trials have demonstrated a survival benefit with the use of implantable cardioverter-defibrillators (ICDs) in this pop-

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Abbreviations and Acronyms

CART = classification and regression tree

CHF = congestive heart failure

DCM = dilated cardiomyopathy

EDD = end-diastolic dimension

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVEF = left ventricular ejection fraction

LVPWT = left ventricular posterior wall thickness

SCD = sudden cardiac death

ulation (2–4). American Heart Association/American College of Cardiology guidelines recommend ICD placement in adults with nonischemic dilated cardiomyopathy (DCM) who have a left ventricular ejection fraction (LVEF) <35% and are in New York Heart Association functional class II or III (5).

The estimated annual incidence of DCM in children is 0.57 cases per 100,000, and the overall prognosis is poor, with 40% of children undergoing cardiac transplantation or dying within 5 years after diagnosis (6). However, the incidence of SCD is low based on single-center reports, yet little information is available on risk factors for SCD (7,8). Therefore, there are no established criteria for the use of ICDs for the primary prevention of SCD in children with DCM.

We determined the incidence and risk factors for SCD using data in a large multicenter cohort of children with DCM. We analyzed the association of demographic, clinical, and echocardiographic characteristics with SCD. We sought to identify the characteristics of children who may benefit from ICD placement for the primary prevention of SCD.

Methods

Study design. The PCMR (Pediatric Cardiomyopathy Registry) has enrolled >3,500 infants, children, and adolescents with cardiomyopathy younger than 18 years of age at diagnosis from nearly 100 pediatric cardiac centers in North America. Children were enrolled retrospectively if they were diagnosed with cardiomyopathy between 1990 and 1995 and prospectively thereafter (9,10). Annual reporting continues until death or heart transplantation.

All centers obtained institutional review board approval for participation in the PCMR.

Study sample. All enrolled patients with DCM in the PCMR met at least 1 of the following criteria (10): 1) strict echocardiographic criteria for DCM (left ventricular [LV] dilation [i.e., LV end-diastolic dimension [EDD] ≥2 SD above normal for body surface area] and depressed LV systolic function [LV fractional shortening or LVEF ≥2 SD below normal for age]); 2) pathologic findings consistent with DCM at autopsy or by endomyocardial biopsy; or 3) other clinical evidence of DCM provided by the cardiologist.

Children with specific secondary causes of myocardial abnormalities were excluded, which included but were not limited to associated congenital heart disease, endocrine disorders known to cause myocardial damage, a history of chemotherapy or pharmacology-associated cardiotoxicity, chronic arrhythmia, pulmonary parenchymal or vascular disease, and immunologic disease.

SCD definition. SCD was defined as an unexpected death occurring <1 h after the onset of a symptomatic cardiac event. The circumstances of death were abstracted from the medical record. Three pediatric cardiologists (E.P., C.E.C., S.D.C.) reviewed the autopsy report where available and the abstracted notes for all deaths to ensure consistent classification. All deaths were classified as either SCD, cardiac death that was non-SCD, or unknown.

Measurements. Demographic information, clinical evidence of CHF, New York Heart Association functional class, family history of cardiomyopathy, medication classes, and other therapies were recorded from the time of cardiomyopathy diagnosis and annually. Echocardiographic measurements were collected from the clinical study performed at the time of presentation and from the most recent clinical echocardiogram obtained during each annual reporting period. These included LV EDD, LV end-systolic dimension, LV fractional shortening, LV septal and LV posterior wall thicknesses, LV mass, and the presence of tricuspid or mitral regurgitation. Information regarding the use of medications other than anticongestive therapy, ICD implantation, valvar regurgitation grade, atrial enlargement, and electrocardiographic, and Holter monitoring findings were primarily collected on retrospectively enrolled patients. In addition, LVEF data collection was limited.

Statistical methods. All data were analyzed by the Data Coordinating Center at the New England Research Institutes, Watertown, Massachusetts. Descriptive statistics include counts and percentages for categorical data, median and interquartile range for highly skewed data, and mean ± SD for normally distributed data. We used mean imputation for all echocardiographic values except LVEF, which was missing for two-thirds of patients. Echocardiographic *z*-scores were calculated relative to body surface area (LV EDD, LV end-systolic dimension, LV end-diastolic posterior wall and septal thicknesses, and M-mode–derived LV mass) or relative to age (LV fractional shortening and LVEF) (11). Electrocardiographic and Holter monitoring data, available in less than one third of subjects, were used in univariate analysis only without imputation.

The primary outcome was SCD. The cumulative incidence rates of SCD, non-SCD, unknown cause of death, and transplantation were estimated using competing risks methodology (12). The 56 deaths of unknown cause were excluded from risk factor analysis. Cox proportional hazards regression modeling was used to identify univariate risk

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factors for SCD. For risk factor modeling, the survival times of all children not experiencing SCD were censored at the date of last known date alive, non-SCD, or transplantation. Candidate predictors included measures from the time of cardiomyopathy diagnosis as well as echocardiographic measurements from the latest available echocardiogram. We developed risk prediction models using recursive partitioning (classification and regression tree [CART]), for the presence or absence of SCD (13). We adopted this approach rather than multivariable regression modeling, in which the patient subgroups required to construct interaction terms would require pre-specification. CART creates nonparametric discriminating trees by dividing patients repeatedly into subgroups, each representing subjects with a low versus high risk of SCD.

Alpha was set at 0.05, and all tests were 2 tailed. Analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and R and S-PLUS version 8.0 (Insightful Corporation, Seattle, Washington).

Results

As of February 2009, the PCMR included 1,803 children with a diagnosis of DCM since 1990. Causes of DCM determined at presentation were idiopathic disease (n = 1,286), myocarditis (n = 255), neuromuscular disorder (n = 136), malformation syndrome (n = 10), familial isolated cardiomyopathy (n = 78), and inborn error of metabolism (n = 38). Mean age at diagnosis was 5.3 ± 6.1 years. Mean LV EDD *z*-score was 4.3 ± 2.7, LV fractional shortening was 16 ± 9%, and LVEF (n = 597) was 28 ± 14%. Median follow-up in patients with no death or transplantation event was 2.6 years (interquartile range, 0.8 to 5.3 years; maximum, 16.7 years).

Event rates. Of 280 deaths, the type of death was SCD in 35 (13%), non-SCD in 189 (68%), and unknown in 56 (20%). Thus, among patients with a known mode of death, 16% were SCD (35 of 224). Among the 1,747 survivors and those with a known cause of death, SCD comprised 1.9%. The majority of SCDs, 74% (n = 26), occurred <2 years after presentation. Most non-SCDs were caused by CHF.

The incidence rate of SCD was low, and the rates of transplantation and non-SCD were high. The 1-, 3-, and 5-year cumulative incidence rates were 1.3%, 2.0%, and 2.4%, respectively (95% CI: 1.7% to 3.4%) for SCD. The 1-, 3-, and 5-year cumulative incidence rates for non-SCD were 8.1%, 10.8%, and 12.1%, and 22%, 27%, and 29%, respectively, for heart transplantation (Fig. 1). In addition, the 5-year incidence of death of unknown cause (n = 56) was 4%. If the proportion of patients who experienced SCD in the group with an unknown cause of death is similar to that in the patients with a known cause of death (16%; 32 of 225), then we estimate that 9 additional patients experienced SCD, and the 5-year cumulative incidence of SCD is 3.0%. This group of 56 patients is not included in risk factor analyses.

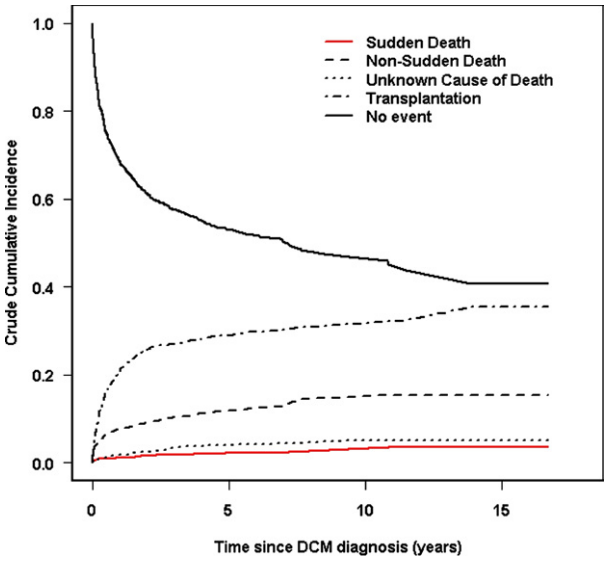

Figure 1 **Competing Risk Analysis: Outcomes in Children With Dilated Cardiomyopathy**

Competing risks analysis for sudden cardiac death, non-sudden cardiac death, unknown cause of death, and cardiac transplantation among 1,803 children with dilated cardiomyopathy (DCM) listed in the Pediatric Cardiomyopathy Registry. The 3-, 5-, and 10-year cumulative incidence rates (95% confidence interval) of sudden cardiac death are estimated to be 2.0% (1.4% to 2.8%), 2.4% (1.7% to 3.4%), and 2.7% (1.8% to 3.9%), respectively; of non–sudden cardiac death, 10.8% (9.3% to 12.4%), 12.1% (10.4% to 13.9%), and 14.9% (12.6% to 17.3%), respectively; and of heart transplantation, 27% (25% to 29%), 29% (27% to 32%), and 31% (28% to 34%), respectively. The rate of death of unknown cause (95% confidence interval) was 3.4% (2.6% to 4.5%), 4.0% (3.0% to 5.2%), and 5.2% (3.6% to 7.3%).

Risk factors for SCD: predictors from the time of cardiomyopathy diagnosis. SCD was not associated with sex, race/ethnicity, or cause of DCM (Table 1). Children who experienced SCD were more likely to present with CHF (86%) at diagnosis than children who did not experience SCD (73%, hazard ratio: 2.84; p = 0.03). In the first month after diagnosis, 47% of the SCD group and 22% of all other children were on antiarrhythmic therapy (hazard ratio: 3.00, 95% confidence interval: 1.08 to 8.30; p = 0.03). Family history of SCD, family history of cardiomyopathy, New York Heart Association functional class, and use anticongestive or beta-blocker agents in the first month after diagnosis were not associated with SCD. Among the subset of 548 patients who had information on ICD therapy, only 9 had an ICD, and none experienced SCD.

We examined echocardiographic parameters obtained at presentation (Table 1). Compared with patients without SCD, patients with SCD had a lower (log-transformed) LVPWT to EDD ratio, an index of ventricular remodeling that is a surrogate for LV end-diastolic wall stress, with a low ratio indicating insufficient LV hypertrophy (p = 0.02). A larger LV posterior wall thickness *z*-score was protective against SCD (hazard ratio: 0.86, p = 0.047). Fractional shortening *z*-score was not a risk factor (p = 0.33).

JACC Vol. 59, No. 6, 2012
February 7, 2012:607–15

Table 1 Patient Characteristics by SCD Status and Univariate Cox Regression Results

	SCD (n = 35)	All Others (n = 1,712)	Hazard Ratio (95% CI)	p Value
Retrospective cohort	28.6	25.3	1.13 (0.53–2.42)	0.752
Age at diagnosis, yrs	4.7 ± 5.6	5.3 ± 6.1	0.99 (0.94–1.05)	0.738
Male	54.3	53.5	1.05 (0.54–2.05)	0.880
Race/ethnicity				0.649
White	62.9	55.3	2.42 (0.33–17.93)	
Black	22.9	21.0	2.55 (0.32–20.37)	
Hispanic	11.4	16.9	1.46 (0.16–13.04)	
Other	2.9	6.8	—	
Idiopathic	77.1	71.6	1.55 (0.70–3.41)	0.279
CHF at diagnosis	85.7	72.6	2.84 (1.10–7.35)	0.031
NYHA functional class IV				0.139
Yes	34.3	23.8	1.79 (0.70–4.56)	
No	20.0	19.6	Ref	
Unknown	45.7	56.5	0.85 (0.35–2.07)	
Family history of cardiomyopathy				0.551
Yes	11.4	12.1	0.74 (0.25–2.18)	
No	51.4	44.9	Ref	
Unknown	37.1	43.0	0.68 (0.33–1.39)	
Family history of sudden death				0.905
Yes	5.7	6.0	0.86 (0.20–3.70)	
No	54.3	52.7	Ref	
Unknown	40.0	41.3	0.86 (0.43–1.72)	
Anticongestive therapy				
Yes	88.6	82.2	1.60 (0.57–4.55)	0.375
No	11.4	14.3	Ref	
Unknown	0	3.5	—	
Antiarrhythmic therapy				0.025
Yes	20.0	12.1	3.00 (1.08–1.30)	
No	22.9	41.4	Ref	
Unknown	57.1	46.5	3.00 (1.31–6.86)	
ACE inhibitor				0.023
Yes	20.0	38.3	0.38 (0.14–1.06)	
No	22.9	18.5	Ref	
Unknown	57.1	43.2	1.30 (0.56–2.98)	
Beta-blocker				0.090
Yes	2.9	7.0	0.30 (0.04–2.27)	
No	40.0	48.0	Ref	
Unknown	57.1	45.0	2.05 (1.02–4.11)	
LV end-diastolic dimension *z*-score	4.2 ± 2.3	4.3 ± 2.4	1.01 (0.88–1.16)	0.928
LV end-systolic dimension *z*-score	5.9 ± 2.2	6.0 ± 2.5	1.01 (0.88–1.16)	0.883
LV fractional shortening *z*-score	−8.8 ± 2.5	−8.5 ± 3.4	0.95 (0.85–1.06)	0.332
LV end-diastolic posterior wall thickness *z*-score	−1.1 ± 2.8	−0.5 ± 2.0	0.86 (0.74–1.00)	0.047
LV end-diastolic septal wall thickness *z*-score	−1.1 ± 1.1	−0.8 ± 1.5	0.84 (0.68–1.05)	0.123
LV mass *z*-score	2.0 ± 2.7	2.3 ± 2.8	0.98 (0.84–1.14)	0.766
LVEF *z*-score*	−6.9 ± 2.5	−6.0 ± 2.4	0.76 (0.55–1.05)	0.094
Raw LVEF*	23.3 ± 14.6	28.5 ± 13.7	0.95 (0.90–1.01)	0.073
LVEF <35%*	8 (80.0)	330 (67.8)	2.69 (0.57–12.69)	0.213
Raw LV fractional shortening, %	15.3 ± 6.2	16.0 ± 8.3	0.97 (0.93–1.02)	0.298
LV fractional shortening <18%	27 (77.1)	1249 (73.0)	1.55 (0.70–3.41)	0.282
Log (ratio of LV posterior wall thickness: end-diastolic dimension)	−2.24 ± 0.38	−2.13 ± 0.32	0.28 (0.10–0.79)	0.016

Continued on next page

Table 1 Continued

	SCD	All Others	Hazard Ratio (95% CI)	p Value
Moderate to severe tricuspid regurgitation				0.078
Yes	8.6	3.7	4.73 (1.13–19.80)	
No	14.3	26.3	Ref	
Unknown	77.1	69.9	2.46 (0.93–6.51)	
Moderate to severe mitral regurgitation, %				0.176
Yes	14.3	9.3	3.33 (0.89–12.40)	
No	11.4	20.9	Ref	
Unknown	74.3	69.9	2.39 (0.82–6.95)	

Values are %, mean ± SD, or n (%). *Imputation was not used for LVEF. Raw LVEF n = 10 for SCD group and 487 for all others. LVEF *z*-score n = 10 for SCD group and 485 for all others.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CI = confidence interval; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; Ref = reference group for hazard; SCD = sudden cardiac death.

We also examined electrocardiographic and Holter findings from the latest available follow-up. Of the 35 SCD patients, 13 had an electrocardiogram but only 5 had quantitative data, with a mean QTc interval of 449 ± 72 ms. None of the 5 had any degree of atrioventricular block. One of the patients had a notation for wide complex tachycardia. These findings were qualitatively very similar to those in the 531 non-SCD patients who had QTc data (428 ± 50 ms), with 5% (21 of 441) having atrioventricular block (none third degree). Holter data were available for 5 of 35 SCD patients, with 3 of 5 (60%) having ventricular tachycardia and 60% having ventricular couplets. In the non-SCD group, 18% (52 of 294) had ventricular tachycardia, and 25% (75 of 295) had ventricular couplets. No patients in either group had third-degree heart block or atrioventricular block. These limited data were not used in multivariable analysis.

Multivariable CART analysis based on predictors from the time of DCM diagnosis demonstrated that the LV posterior wall thickness *z*-score, age at diagnosis, and LV septal thickness *z*-score and antiarrhythmic therapy are the most important discriminators between SCD and non-SCD (Fig. 2). Overall, 2% of subjects had SCD. Two of the 5 subgroups in the regression tree have at least twice the risk of SCD (e.g., >4 %). These include: 1) patients with LV posterior wall thickness *z*-score <-1.7; and 2) patients with LV posterior wall thickness *z*-score ≥-1.7, age at diagnosis younger than 13.1 years, septal thickness *z*-score <-0.8, and those who were prescribed antiarrhythmic therapy within a month of presentation with DCM. This model classified 24% of patients as high risk (i.e., 20 of 35 deaths occurred in these groups), yielding 57% sensitivity and 78% specificity. Due to the very low prevalence of SCD, the positive predictive value (percentage of % SCD among those identified as high risk) was only 5%, whereas the negative predictive value (percentage of non-SCD among those identified as lower risk) was 99%.

Risk factors for SCD: predictors from last available follow-up. Because treatment decisions are made based on the most current status of the patient, we also examined the predictive strength of the latest available measures of LV size and function. More than three-fourths (78%) of subjects had at least 1 follow-up measurement (range, 1 to 17). For the remainder, their value from the time of diagnosis was used.

Univariate analysis (Table 2) shows that a higher risk of SCD was significantly associated with all echocardiographic parameters except for LV posterior wall and septal thicknesses. For LV EDD and mass, a unit increase in *z*-score was associated with a 1.2- to 1.3-fold increase in risk. Similarly, a 5-unit decrease in LV fractional shortening (%) or LVEF (%) imparted a 1.4- to 1.5-fold increase in the risk of SCD. The LVPWT:EDD ratio was again highly predictive ($p < 0.001$). At least moderate mitral (3% of patients) or tricuspid (8% of patients) regurgitation was also associated with SCD.

Multivariable CART analysis that considered echocardiographic measurements from the most recent follow-up (except for LVEF, see the Methods section) in addition to age and the presence of CHF at diagnosis demonstrated that LV end-systolic dimension *z*-score, age at diagnosis, and LVPWT:EDD ratio are the most important discriminators between SCD and non-SCD (Fig. 3). The tree had 4 terminal nodes. Three nodes had a below-average rate of SCD (0% to 1.8%). A single node captured 30 of the 35 SCD. This subgroup (44% of patients) with the highest SCD rate (3.9%, 30 of 766) met all 3 of the following criteria: 1) LV end-systolic dimension *z*-score >2.6; 2) DCM diagnosis at age younger than 14.3 years; and 3) LVPWT:EDD ratio <0.14. This patient subset produced high sensitivity of 86% (30 of 35) and specificity of 57% (981 of 1,712), albeit with a positive predictive value of 4% and a negative predictive value of 99%.

Despite the LVEF from follow-up being available for only 46% of patients, we examined the predictive strength of LVEF <35%, a commonly used threshold, and assessed its validity by comparing it with the equivalent value of LV fractional shortening <18%. The results for these 2 thresholds were similar (Table 2). If an LVEF <35% is used as an indication for ICD placement, sensitivity is only 73% (compared with the regression tree result in Figure 3 with 86% sensitivity). Spec-

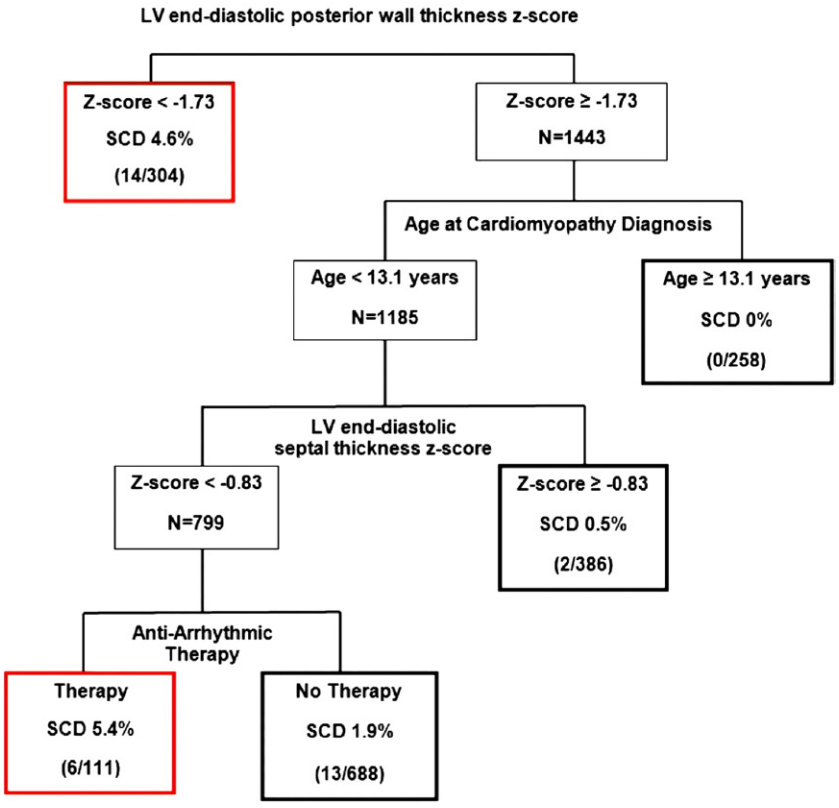

Figure 2 Classification and Regression Tree for SCD

Predictors from time of cardiomyopathy diagnosis (N = 1,747, 35 sudden cardiac deaths [SCD]). **Red boxes** denote high-risk patient groups. **Bold black boxes** denote lower risk patient subgroups. Sensitivity = 57%, specificity = 78%. False-positive rate = 95%, false-negative rate = 1.1%. LV = left ventricular.

ificity using an LVEF <35% was the same as that yielded by the regression tree (57%).

Discussion

Incidence of SCD. Our first goal was to determine the incidence of SCD in a large cohort of well-characterized children with DCM. We found that the 5-year cumulative incidence of known SCD in patients with DCM is 2.4%. If the proportion of SCD in the patients who died of unknown causes was similar to the proportion in the patients who died of known causes, the estimated 5-year incidence rate of SCD is 3%. In a series of 85 children with DCM (mean LVEF, 25%), only 1 child (1%) died suddenly (7). In multicenter study of SCD by Rhee et al. (14) in 2,392 children with DCM and congenital heart disease listed for transplantation, the incidence of SCD was low (1.3%), and only those patients with ischemic cardiomyopathy had an increased risk of SCD (relative risk, 6.92).

The incidence of SCD is well below the rates reported in adults with DCM (15). In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial, SCD occurred in 7.4% of 458 adults with DCM (with LVEF 36%); the mortality rate at 2 years was 14.1% in the standard therapy group (annual mortality of 7%) compared with 7.9 % in the ICD group (2). Thus, in children with DCM, in contrast to adults, SCD is rare, and death caused by progressive CHF is more common (7,15,16). The reason for this lower incidence in SCD is unclear, but may be due to several factors. Children have fewer ventricular arrhythmias documented by ambulatory Holter monitoring than do adults with idiopathic DCM (1–3,5,7,8). Fibrosis has been shown to correlate with ventricular arrhythmias and SCD (17), and children with DCM may have less fibrosis than adults with DCM due to age-related factors as well as age-dependent comorbidities such as diabetes and hypertension. These comorbidities in adults lead to diastolic dysfunction that may have additive effects that lead to more ventricular arrhythmias in adults with DCM; thus, DCM in children may have a different natural history than that in adults. Our study has shown that deaths in children with DCM are typically due to CHF or graft loss occurring from transplantation rather than SCD, suggesting a different pathophysiology than in adults. More research with biomarkers and genotype-phenotype correlations will be necessary to better define the natural history that differentiates DCM presenting in children from that observed in adults.

Table 2 Patient Characteristics by SCD Status Using Measurements From the Last Follow-Up and Univariate Cox Regression Results

	SCD	All Others	Hazard Ratio (95% CI)	p Value
CHF	77.1	50.6	7.89 (3.47–17.96)	0.002
Echocardiographic measurements				
LV end-diastolic dimension *z*-score	4.8 ± 2.6	3.3 ± 2.8	1.31 (1.17–1.48)	<0.001
LV end-systolic dimension *z*-score	6.3 ± 2.4	4.4 ± 3.5	1.30 (1.17–1.44)	<0.001
LV fractional shortening *z*-score	−8.2 ± 3.5	−5.4 ± 4.8	0.78 (0.71–0.86)	<0.001
LV end-diastolic posterior wall thickness *z*-score	−0.6 ± 2.2	−0.7 ± 2.1	1.05 (0.91–1.23)	0.494
LV end-diastolic septal thickness *z*-score	−1.1 ± 1.1	−0.9 ± 1.7	0.94 (0.76–1.15)	0.532
LV mass *z*-score	2.6 ± 2.3	1.6 ± 2.4	1.21 (1.10–1.32)	<0.001
LV ejection fraction *z*-score*	−6.3 ± 1.6	−5.1 ± 2.4	0.69 (0.57–0.83)	<0.001
Raw LV ejection fraction, %*	27.0 ± 8.8	33.7 ± 14.1	0.94 (0.91–0.97)	<0.001
LV ejection fraction <35%*	11 (73.3)	336 (42.6)	8.67 (2.71–27.72)	<0.001
Raw LV fractional shortening	16.2 ± 8.5	22.1 ± 12.0	0.92 (0.88–0.95)	<0.001
LV fractional shortening <18%	25 (71.4)	789 (46.1)	5.63 (2.64–11.97)	<0.001
Log (ratio of LV posterior wall thickness: end-diastolic dimension)	−2.2 ± 0.30	−2.1 ± 0.3	0.19 (0.08–0.46)	<0.001
Moderate to severe tricuspid regurgitation				0.001
Yes	17.1	7.9	9.86 (2.76–18.94)	
No	11.4	33.1	Ref	
Unknown	71.4	58.9	6.26 (2.07–18.94)	
Moderate to severe mitral regurgitation				0.005
Yes	5.7	2.8	6.44 (1.32–31.29)	
No	20.0	38.3	Ref	
Unknown	74.3	59.0	4.09 (1.66–10.07)	

Values are %, mean ± SD, or n (%). *Raw LVEF n = 15 for SCD group and 789 for all others. LVEF *z*-score n = 15 for SCD group and 787 for all others.
Abbreviations as in Table 1.

Risk factors for SCD: factors known at diagnosis. Our second goal was to develop a risk stratification rule to identify children at high risk of SCD to aid clinicians in identifying those patients who may benefit from ICD placement. Sex, race/ethnicity, cause of DCM, family history, and LV fractional shortening were not independent risk factors. Our multivariable CART analysis showed that 24% of children fell into a high-risk group based solely on factors known at presentation. One high-risk group was defined solely by a thin-walled left ventricle at presentation (LV posterior wall thickness *z*-score <-1.7) and the other by patients with LV wall thickness above this cutoff but who received a diagnosis before 13.1 years, had a thin LV septum, and were prescribed antiarrhythmic therapy in the month that DCM was diagnosed. These findings stress the value of intraventricular septal thickness and LV posterior wall thickness observed early in the course of DCM in children. Basing ICD implantation decisions on these criteria captured more than one-half of patients who went on to have SCD.

The use of antiarrhythmic medications within 30 days of presentation was a risk factor for SCD in the CART analysis tree as well as in the univariate analysis. The type of antiarrhythmic agent was not collected for most subjects. Arrhythmia in adults with poor LV function is a risk factor for SCD and has been used as an indication for placing ICDs, and children with a history of sustained ventricular tachycardia or ventricular fibrillation are more likely to undergo ICD placement. In our study, arrhythmia data were not consistently collected and 24-h Holter monitoring data were not routinely available, so these could not be examined as risk factors. A single-center study of 63 children with DCM found that 46% had arrhythmias; the majority were atrial, and only 6 had ventricular tachycardia (8). Death occurred in 4 of the 29 children with known arrhythmias; however, only 1 of these children died suddenly.

Of note, moderate to severe tricuspid and mitral insufficiency at latest follow-up were more frequently identifiable in the SCD cohort on univariate analysis. Tricuspid regurgitation typically correlates with more severe CHF and is likely a surrogate for pulmonary hypertension (18).

Risk factors for SCD: last available follow-up. With the use of clinical information from the last available follow-up, we constructed a risk stratification model with high sensitivity (86%) and moderate specificity (57%). A single node of the CART captured 30 of the 35 SCDs. These patients had an increased systolic ventricular size (LV end-systolic dimension *z*-score >2.6) indicating abnormal dilation, were younger than 14 years old at diagnosis, and had a decreased LVPWT:EDD ratio (<0.14). This prediction rule is easy to use and based on measurements performed (or calculable) from routine echocardiography. A lower LVPWT:EDD ratio was also found in univariate analyses to be associated with the composite endpoint of all-cause mortality and transplantation in the PCMR DCM cohort (6). We hypothesize that patients with a low LVPWT:EDD ratio may have an insufficient LV hypertrophic response to compensate for the LV dilation caused by the

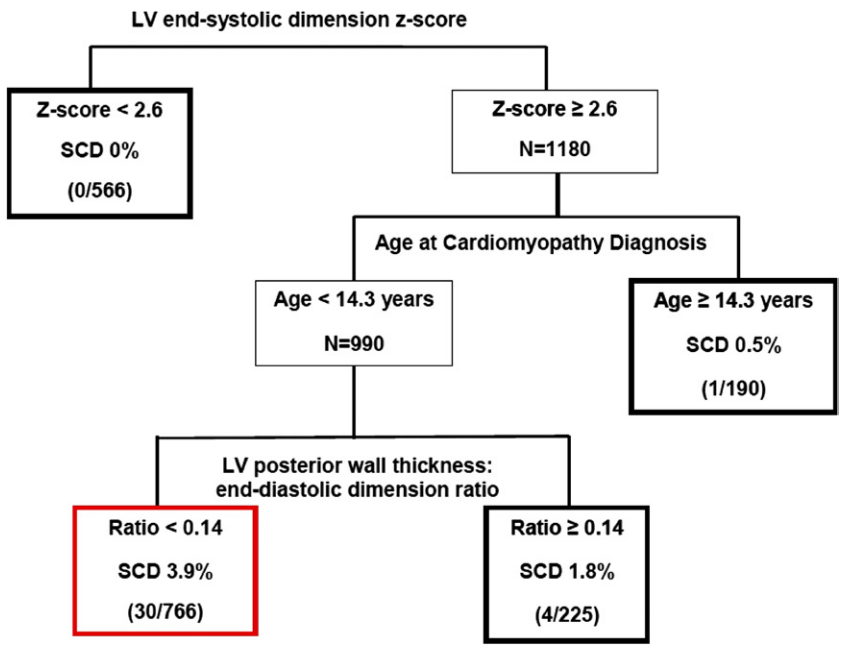

Figure 3 Classification and Regression Tree for SCD

Predictors from time of last follow-up (N = 1,747, 35 SCDs). **Red box** denotes the high-risk patient group. **Bold black boxes** denote lower risk patient subgroups. Sensitivity = 86%, specificity = 57%. False-positive rate = 96%, false-negative rate = 0.6%. Abbreviations as in Figure 2.

cardiomyopathy. Monitoring of disease progression and associated changes in the risk of SCD is recommended because a patient's echocardiographic measurements of LV size may worsen or improve over time.

This risk stratification model may be used independently or in conjunction with the first at diagnosis tree to identify children with DCM who are at higher risk of SCD for whom increased monitoring is appropriate. If the first tree (rule) is used, then 24% of children with DCM would receive an ICD at the time of diagnosis of cardiomyopathy. With the use of the second tree, eventually 44% of subjects might receive an ICD, with only 4% of those receiving an ICD truly at risk of an event—that is, 26 patients would undergo ICD implantation to prevent 1 event of SCD. Considerable tradeoffs therefore continue to exist with respect to ICD placement, but our estimated low incidence of SCD combined with the ability to moderately discriminate risk levels suggests that universal ICD implantation in the pediatric DCM population is probably not warranted.

Whether ICDs could be beneficial in higher risk children is unclear. In a review of ICD databases at 9 heart transplantation centers, Dubin et al. (19) reported that 28 patients received ICDs while awaiting transplantation (16 had DCM). Of these, 42% had an appropriate discharge; however, the incidence of inappropriate ICD discharge was 25%.

The model presented here provides evidence that ICD implantation is not indicated for all children presenting with DCM and demonstrates that those at highest risk can be identified. However, the successful identification of the children at highest risk of SCD, a relatively rare event, lacks specificity, with 26 ICD implantations required to prevent 1 SCD. Therefore, recommendations for ICD placement in children must be considered in conjunction with the concomitant anxiety related to inappropriate shocks, as well as an increased likelihood of complications such as lead fractures and the need for frequent lead and defibrillator replacement, and body size issues that necessitate epicardial rather than transvenous systems in smaller children (20). Clinical decision making is a continuous process and uses cumulative evidence regarding a patient's condition that is garnered across multiple follow-ups. If a child who received a diagnosis of DCM before 14 years of age consistently meets all the criteria that indicate a high risk of SCD (abnormal LV end-systolic dimension *z*-score and LVPWT:EDD ratio <0.14), ICD implantation should be considered. Definitive criteria for ICD use in children must await clear evidence of improved survival based on these criteria.

Study limitations. First, 56 of 280 deaths did not have an identifiable cause of death. Although some of these deaths may have been sudden rather than due to CHF, we hypothesize that, for most, it is a random sample of deaths with missing information. Therefore, we reported a secondary estimate of SCD incidence that incorporated 16% of the deaths with unknown cause into the event rate estimate. The estimated 5-year rate was still only 3%.

Another limitation is the lack of information about the incidence of ventricular arrhythmias in this population. Ventricular arrhythmias are a risk factor for SCD in adults

with DCM. However, only 9 of 538 patients with therapy data available had undergone an ICD placement; thus, it is unlikely that ventricular arrhythmias were common in this population. Furthermore, unlike in adult patients, invasive electrophysiologic stimulation is not performed routinely in children to assess the risk of sustained monomoprhic ventricular tachycardia. Therefore, it is possible that the components of the risk stratification model would differ if this information were available.

Similarly, electrocardiographic and Holter monitoring data were not included in our multivariable analyses because they were collected for <15% of the SCD patients and less than one-third of the patients without SCD. Some of the missing data are due only to the timing of the data collection protocol and thus are possibly missing at random; however, other causes of not undergoing electrocardiography or Holter monitoring that may render those with data to be a nonrepresentative subset cannot be dismissed.

We chose to use CART methodology, due in part to the visual appeal of the classification tree and ease of interpretation and application for clinicians. However, we note as a limitation that CART has been shown to have a similar and not necessarily superior predictive power relative to other risk stratification methods, such as logistic regression and machine learning approaches (21). If our data were analyzed using a different approach, it is possible that a different set of discriminatory factors might be identified. The final limitation is that the risk stratification models presented have not been validated using an independent dataset. Application of these models to other DCM cohorts will provide needed evidence of its accuracy and reliability.

Conclusions

The 5-year incidence of SCD in children with DCM does not exceed 3%, a rate much lower than in adults. Independent predictors of SCD include echocardiographic features of both LV thinning and dilation, the LVPWT:EDD ratio, use of antiarrhythmic therapy within 1 month of diagnosis, and age at diagnosis before 13 to 14 years. SCD can be predicted with 86% sensitivity, although with lower specificity (57%), and requires 26 ICD implantations to prevent 1 SCD. Our data support the concept that universal implantation of ICDs is probably not warranted. However, risk stratification is possible and is strengthened by a patient's condition meeting all the high-risk criteria for an extended period. In such situations, ICD placement should be considered for pediatric patients with DCM.

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