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Recovery of Echocardiographic Function in Children With Idiopathic Dilated Cardiomyopathy

Results From the Pediatric Cardiomyopathy Registry

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Objectives This study sought to determine the incidence and predictors of recovery of normal echocardiographic function among children with idiopathic dilated cardiomyopathy (DCM).

Background Most children with idiopathic DCM have poor outcomes; however, some improve.

Methods We studied children <18 years of age from the Pediatric Cardiomyopathy Registry who had both depressed left ventricular (LV) function (fractional shortening or ejection fraction *z*-score <−2) and LV dilation (end-diastolic dimension [LVEDD] *z*-score >2) at diagnosis and who had at least 1 follow-up echocardiogram 30 days to 2 years from the initial echocardiogram. We estimated the cumulative incidence and predictors of normalization.

Results Among 868 children who met the inclusion criteria, 741 (85%) had both echocardiograms. At 2 years, 22% had recovered normal LV function and size; 51% had died or undergone heart transplantation (median, 3.2 months), and 27% had persistently abnormal echocardiograms. Younger age (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.88 to 0.97) and lower LVEDD *z*-score (HR: 0.78; 95% CI: 0.70 to 0.87) independently predicted normalization. Nine children (9%) with normal LV function and size within 2 years of diagnosis later underwent heart transplantation or died.

Conclusions Despite marked LV dilation and depressed function initially, children with idiopathic DCM can recover normal LV size and function, particularly those younger and with less LV dilation at diagnosis. Investigations related to predictors of recovery, such as genetic associations, serum markers, and the impact of medical therapy or ventricular unloading with assist devices are important next steps. Longer follow-up after normalization is warranted as cardiac failure can recur. (Pediatric Cardiomyopathy Registry; NCT00005391) (J Am Coll Cardiol 2014;63:1405–13) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
DCM = dilated cardiomyopathy
EDD = end-diastolic dimension
EF = ejection fraction
ESD = end-systolic dimension
FS = fractional shortening
HR = hazard ratio
LV = left ventricular

Idiopathic dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by ventricular chamber enlargement and systolic dysfunction (1,2). The prognosis is usually poor, but some patients do recover normal cardiac function. Studies in both adults and children have reported recovery of cardiac function in 21% to 37% of patients, as indicated by serial echocardiograms (3–5). Survival of adults with idiopathic DCM has improved in recent decades, with more than half surviving for 10 years (5,6). Although risk factors for death or transplantation in children with idiopathic DCM are well-studied, predictors of normalization are largely unknown (7–10). With additional medical therapies being used for heart failure in children, as well as a marked increase in the use of ventricular assist devices, identifying predictors of recovering cardiac function is of particular importance.

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We studied children with idiopathic DCM who had echocardiographic data sufficient to assess recovery of normal LV function and size. We identified the proportion of these children who regained normal echocardiographic measurements in the large, multicenter, National Heart, Lung, and Blood Institute–funded Pediatric Cardiomyopathy Registry (PCMR) (11,12). We sought to identify the clinical characteristics at presentation that predict echocardiographic normalization within 2 years. Additionally, we report longer-term follow-up data in children whose LV function and size returned to normal within 2 years of diagnosis to examine the permanence of recovery.

Methods

Study design. The design and conduct of the PCMR are detailed elsewhere (13,14). Institutional review board approval of the PCMR protocol was obtained from all participating centers. From 1990 to 2012, the PCMR enrolled more than 3,000 children <18 years of age in whom cardiomyopathy was diagnosed at any of 98 pediatric cardiac centers in the United States and Canada. The data in the PCMR database current as of January 14, 2013, were analyzed.

Patient classification. The PCMR diagnostic criteria for pure DCM (13,14) are based on strict echocardiographic measurements related to left ventricular (LV) enlargement and depressed function; pathologic findings at autopsy or by endomyocardial biopsy; or clinical evidence from the diagnosing physician. We studied only children with *idiopathic DCM,* defined as DCM of unknown cause at the time of diagnosis (1,6,9). Children who were classified at presentation by the clinical investigators as having neuromuscular disease, familial cardiomyopathy, metabolic or mitochondrial disorder, or myocarditis on the basis of the presentation of new-onset cardiac symptoms and/or echocardiographic abnormalities developing after a history of recent infection with or without evidence of myocarditis on endomyocardial biopsy were excluded (4). Additionally, to examine recovery of normal LV function and size in a homogeneous group, the sample was restricted to children who had both 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 [FS] or LV ejection fraction [EF] >2 SD below normal for age) at diagnosis. Echocardiographic outcomes were determined only in children with echocardiographic data on function and size both at diagnosis and at follow-up within 2 years. A minimum interval of 30 days between the first and subsequent echocardiograms was used to classify children into 2 groups: 1) those with persistently abnormal echocardiograms; and 2) those who recovered normal LV size and function. Figure 1 details the composition of the analytic cohort. Echocardiographic data beyond 2 years was not sufficiently complete to uniformly assess a longer follow-up period for recovering normal echocardiographic function and size. However, long-term follow-up data regarding death or heart transplantation outside the 2-year window, where available, are reported for each group.

Data collection. Patient age, race, sex, weight, height, and body surface area were collected at diagnosis. Clinical evidence of congestive heart failure and echocardiographic measurements of LVEDD, left ventricular end-systolic dimension (LVESD), LVFS, LV septal and posterior wall thicknesses, and LV mass were also collected at diagnosis and annually thereafter. Values for LV measurements are expressed as *z*-scores to adjust for the effect of body size and age. The z-score is the number of SDs from the mean value at a given body surface area in a distribution of a large population of normal children. The *z*-score for the mean of this population distribution is 0, and the normal range is typically defined as −2 to +2 SD (10).

Statistical methods. The Data Coordinating Center at the New England Research Institutes, Watertown, Massachusetts, performed all data analyses. Summary statistics are presented as mean ± SD or as median and interquartile range for continuous variables and as percentages for categorical variables. Changes in echocardiographic measures obtained at diagnosis and follow-up were compared using a paired Student *t* test. Patient characteristics among the 3 groups were compared with analysis of variance or the Kruskal-Wallis test for continuous variables and a Fisher exact test for categorical variables.

We used nonparametric competing-risks methodology to estimate the cumulative incidence rates of echocardiographic normalization versus death or transplantation versus persistent abnormal LV size or function (15). Risk factors for the

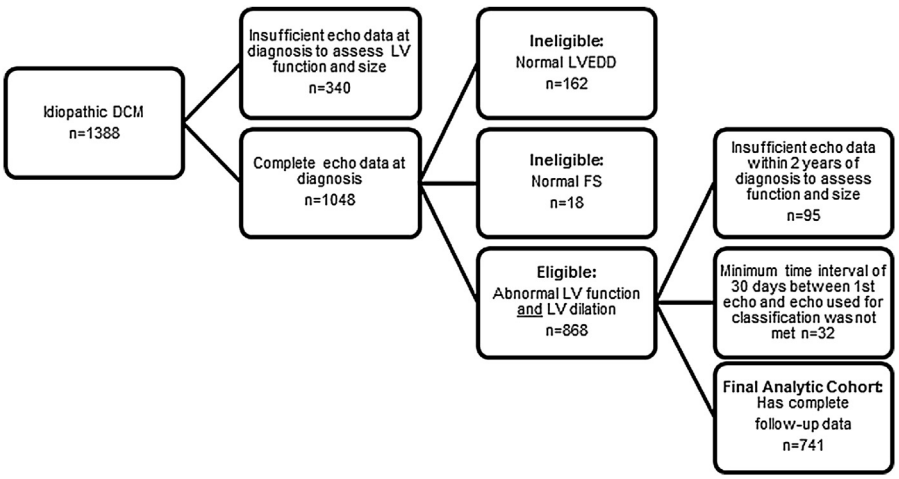

Figure 1 **Echocardiographic Normalization in Children With Idiopathic DCM (N = 741)**

Sample selection to identify echocardiographic normalization in children with idiopathic dilated cardiomyopathy (DCM). FS = fractional shortening; LVEDD = left ventricular end-diastolic dimension.

outcome of echocardiographic normalization in the presence of death or transplantation as a competing risk were also identified using this methodology. Candidate predictors for the multivariate model were variables with a univariate p value <0.2 and had few missing data. A p value <0.05 was considered to be statistically significant. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) or R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria), including the cmprsk library.

Results

Among 1,388 children with idiopathic DCM diagnosed between 1990 and 2012, 868 met the echocardiographic inclusion criteria of both depressed LV systolic function and LV dilation (Fig. 1). Of these, 741 (85%) had sufficient follow-up data 30 days to 2 years following diagnosis and were included in the analysis. The 127 with insufficient follow-up data were slightly older at diagnosis (median [interquartile range]: 2.0 [0.6 to 8.4] years vs. 1.0 [0.3 to 8.1] years; p = 0.01). Of the 741 in the analytic cohort, 96 were classified as achieving normalization of LV size and function on the basis of echocardiographic data, 317 died or underwent heart transplantation, and 328 were classified as having persistently abnormal LV size and/or function.

Patient characteristics. Children with normal echocardiograms within 2 years after diagnosis were younger at diagnosis (Table 1). The normalized group had less LV dilation at diagnosis and a higher mean fractional shortening *z*-score than did the persistently abnormal group and the death/heart transplantation group (Table 2).

In the normalized group, mean LV size, which was more than 4 SD above normal at diagnosis, had a mean *z*-score of −0.06 on follow-up echocardiography, and the fractional shortening *z*-score improved from a mean of −9.21 to close to zero (−0.08). In absolute terms, mean LV fractional shortening increased from 15% to 37%. In the death/transplantation group, baseline and follow-up echocardiographic measurements for LV size and function did not change. In the persistently abnormal group, LV function improved slightly and LV size and mass decreased, but not enough to be considered normal (Table 3).

Outcomes. During the 2-year follow-up period, 22% of children had echocardiographic evidence of both normal LV function and size. The cumulative incidences of the 3 competing outcomes (echocardiographic normalization, death/transplantation, and persistently abnormal LV function or LV dilation) are shown in Figure 2. In the 96 children with normal LV function and size during the 2-year period, the median time to recovering normal echocardiographic function and size was 9.5 months. Seven of these children subsequently underwent heart transplantation. The time interval between the echocardiogram showing normal LV size and function and heart transplantation was between 2 weeks and 10 months in 6 children and 1.75 years in 1 child. Two additional children died at 3.4 and 10.8 years after diagnosis. A subset (n = 51) of the remaining normalized cases had echocardiographic data later than 2 years. Ten (20%) had follow-up measurements that indicated only abnormal LV size or function but not both.

In the 328 children who had persistently abnormal echocardiograms within 2 years of diagnosis, the mean ± SD time from diagnosis to the latest echocardiogram within the 2-year period was 16 ± 7 months. In this group,

Table 1 Characteristics of Children With Idiopathic DCM at Diagnosis (N = 741), by Echocardiographic Status or Clinical Outcome Within 2 Years After Diagnosis

	Normalized (n = 96)	Death or Transplantation (n = 317)	Persistently Abnormal (n = 328)	p Value
Follow-up since diagnosis, median, months	9.5	3.2	17.7	–
Age at diagnosis				
Mean ± SD, yrs	2.4 ± 4.0	5.4 ± 6.0	3.7 ± 5.3	<0.001
Median, yrs	0.93	1.67	0.91	<0.001
Age group, %				<0.001
<1 yrs	55.2	42.9	53.4	
1–10 yrs	35.4	26.8	29.3	
>10 yrs	9.4	30.3	17.4	
Height-for-age, mean ± SD, *z*-score	−0.64 ± 1.74 (n = 47)	−0.52 ± 1.69 (n = 193)	−0.32 ± 1.48 (n = 208)	0.30
Race, %				0.07
White	53.8	55.6	53.7	
Black	16.1	23.8	22.2	
Hispanic	25.8	15.2	15.1	
Other	4.3	5.4	9.0	
Male, %	43.8	49.2	45.4	0.50
Era of diagnosis, %				0.50
1990–1999	60.4	62.5	57.9	
2000–2010	39.6	37.5	42.1	
Congestive heart failure at diagnosis, %	74.0	88.3	69.4	<0.001

DCM = dilated cardiomyopathy.

45 children underwent heart transplantation or died outside the 2-year analysis window, during a median follow-up time of 3 years from diagnosis.

In the 317 children in the death/transplantation group, 104 died and 213 underwent heart transplantation within 2 years after diagnosis of idiopathic DCM. In these 317 children, the median time to death or transplantation was 3 months after diagnosis.

Predictors at diagnosis of echocardiographic normalization. On univariate analysis, *z*-scores for LVEDD, LVESD, LVFS, and LV mass were associated with normalization (Table 4). Multivariate analysis identified age at diagnosis

Table 2 Left Ventricular Echocardiographic Profile at Diagnosis in Children With Idiopathic DCM and Abnormal Left Ventricular Function and Dilation at Diagnosis (N = 741), by Echocardiographic Status or Clinical Outcome Within 2 Years After Diagnosis

	Normalized (n = 96)	Death or Transplantation (n = 317)	Persistently Abnormal (n = 328)	p Value
LV dimension, mean ± SD, *z*-score				
EDD	4.56 ± 1.87	5.70 ± 2.06	5.41 ± 2.06	<0.001
ESD	6.39 ± 2.03 (n = 87)	7.69 ± 1.95 (n = 287)	7.20 ± 2.09 (n = 293)	<0.001
LVFS				
Mean ± SD, *z*-score	−9.21 ± 2.86 (n = 90)	−10.28 ± 2.28 (n = 297)	−9.34 ± 2.81 (n = 313)	<0.001
Mean ± SD, %	15.4 ± 6.9	11.4 ± 4.9	14.7 ± 6.3	<0.001
LVWT, mean ± SD, *z*-score				
Posterior	−0.16 ± 2.29 (n = 81)	−0.39 ± 2.57 (n = 238)	−0.45 ± 2.56 (n = 257)	0.65
Septal	−0.77 ± 1.46 (n = 79)	−0.94 ± 1.73 (n = 217)	−0.88 ± 1.88 (n = 240)	0.77
Mass, mean ± SD, *z*-score	2.71 ± 1.85 (n = 81)	3.42 ± 2.53 (n = 238)	3.11 ± 2.23 (n = 257)	0.046
PWD:EDD ratio, mean ± SD	0.13 ± 0.04 (n = 81)	0.12 ± 0.07 (n = 238)	0.12 ± 0.04 (n = 257)	0.18
Ratio PWT:EDD *z*-score	−1.80 ± 1.48 (n = 81)	−2.23 ± 2.31 (n = 238)	−2.17 ± 1.48 (n = 257)	0.18

DCM = dilated cardiomyopathy; EDD = end-diastolic dimension; ESD = end-systolic dimension; LVFS = left ventricular fractional shortening; LVWT = left ventricular wall thickness; PWT = posterior wall thickness.

Table 3 Left Ventricular Echocardiographic Profile From Time of Cardiomyopathy Diagnosis to 2 Years in Children With Idiopathic Dilated Cardiomyopathy and Abnormal Left Ventricular Function and Dilation at Diagnosis (N = 741), by Echocardiographic Status or Clinical Outcome Within 2 Years After Diagnosis

	Normalized		Death or Transplant		Persistently Abnormal	
	At Diagnosis (n = 96)	Follow-Up Echocardiogram* (n = 96)	At Diagnosis (n = 317)	Follow-Up Echocardiogram* (n = 202)	At Diagnosis (n = 328)	Follow-Up Echocardiogram* (n = 328)
LV dimension, *z*-score						
EDD	4.56 ± 1.87	−0.06 ± 4.25	5.70 ± 2.06	6.05 ± 2.34	5.41 ± 2.06	3.43 ± 2.63
ESD	6.39 ± 2.03	−0.17 ± 3.56	7.69 ± 1.95	7.79 ± 2.37	7.20 ± 2.09	4.40 ± 3.06
LVFS						
z-score	−9.21 ± 2.86	−0.08 ± 1.74	−10.28 ± 2.28	−9.79 ± 3.14	−9.34 ± 2.81	−5.49 ± 3.67
%	15.40 ± 6.88	37.12 ± 4.76	11.44 ± 4.92	12.60 ± 7.19	14.65 ± 6.33	23.16 ± 9.14
LVWT, *z*-score						
PWT	−0.16 ± 2.29	−0.58 ± 1.84	−0.39 ± 2.57	0.15 ± 2.29	−0.45 ± 2.56	−0.74 ± 2.64
SWT	−0.77 ± 1.46	−0.53 ± 1.40	−0.94 ± 1.73	−0.75 ± 1.49	−0.88 ± 1.88	−0.81 ± 1.90
Mass, *z*-score	2.71 ± 1.85	−0.35 ± 1.83	3.42 ± 2.53	3.89 ± 2.44	3.11 ± 2.23	1.55 ± 2.60
PWT:EDD						
Ratio	0.13 ± 0.04	0.18 ± 0.13	0.12 ± 0.07	0.13 ± 0.05	0.12 ± 0.04	0.14 ± 0.08
z-score	−1.80 ± 1.48	−0.26 ± 4.66	−2.23 ± 2.31	−1.94 ± 1.88	−2.17 ± 1.48	−1.62 ± 2.63

Values are mean ± SD. *Follow-up echocardiogram defined as the first occurrence of normalization in the normalized group; the latest echocardiogram before death/transplantation in the death/transplantation group; or the latest echocardiogram within 2 years following diagnosis in the persistently abnormal group.

Abbreviations as in Table 2.

(hazard ratio: 0.92; 95% confidence interval: 0.88 to 0.97) and LV dilation (a lower LVEDD *z*-score; i.e., closer to normal; hazard ratio: 0.78; 95% confidence interval 0.70 to 0.87) as the 2 independent factors associated with a higher likelihood of recovering normal LV size and function by echocardiogram within 2 years after diagnosis. For each 1-year decrease in age at diagnosis, children were 1.1-fold more likely to recover normal LV size and function within 2 years of diagnosis (hazard ratio [HR]) (95% CI: 1.05 to 1.16; $p < 0.001$). For every 1-unit decrease in LVEDD *z*-score, the likelihood of recovering normal LV size and function within 2 years of diagnosis was 1.3-fold higher (HR) (95% CI: 1.19 to 1.47; $p < 0.001$).

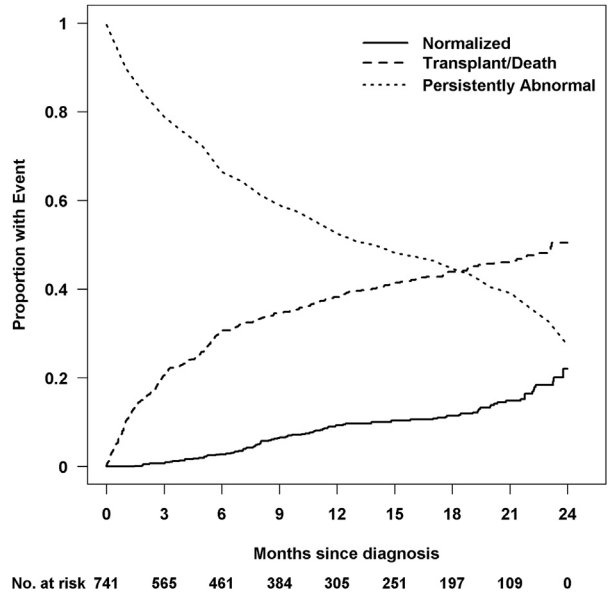

Figure 2 Cumulative Incidence of Echocardiographic Normalization in Children With Idiopathic DCM (N = 741), in the Presence of the Competing Risk for Death or Transplantation

At any given time point, the estimated cumulative incidence rates associated with the 3 states totals to 1.0. At 2 years, 22% of children had normal echocardiographic values, 51% had died or undergone transplantation, and 27% remained abnormal with respect to LV size and function.

Cumulative incidences of recovering normal LV size and function by age are shown in Figure 3. Younger age at diagnosis, as both a continuous and a categorical variable (<1, 1–10, or >10 years), was associated with a higher incidence of normalization ($p < 0.001$ and $p = 0.008$, respectively). Normalization by 2 years was achieved in 24% of infants and in 26% of children aged 1 to 10 years, but in only 10% of those diagnosed after age 10 years. Figure 4 shows the cumulative incidences of having a normal echo within 2 years of diagnosis on the basis of LVEDD *z*-score at diagnosis. Normalization with respect to LV size and function was achieved in 30% of children with LVEDD *z*-scores in the lowest tertile (<4.29), in 21% of those in the middle tertile, and in 13% of those with LVEDD *z*-score in the highest tertile (≥6.29). Event probabilities were similar when displayed according to LVESD *z*-score.

We conducted a sensitivity analysis to assess whether potential misclassification arising from the use of follow-up echocardiograms obtained before but not precisely at the 2-year time target affected the robustness of the multivariate model. Of the 328 children classified as having persistently abnormal echocardiograms, 204 had an echocardiogram beyond the 2-year time period of interest. No subsequent echocardiograms were available in 124 children classified as

Table 4 Hazard Ratios From Univariate Cox Regression Analysis of Possible Predictors of Echocardiographic Normalization in Children With Idiopathic Dilated Cardiomyopathy and Abnormal Left Ventricular Function and Dilation at Diagnosis (N = 741)

Characteristic at Diagnosis	Hazard Ratio (95% CI)	p Value
Age (N = 741), yrs*	0.92 (0.88–0.97)	<0.001
Age group		0.008
<1 yrs	2.77 (1.38–5.57)	
1–10 yrs	3.05 (1.48–6.28)	
>10 yrs	Reference	
Male (N = 741)	0.88 (0.59–1.31)	0.52
Body surface area *z*-score (n = 715)	1.11 (0.97–1.27)	0.12
Height-for-age *z*-score (n = 448)	0.92 (0.78–1.09)	0.35
Race (N = 741)		0.07
White	0.94 (0.42–2.10)	
Black	0.65 (0.27–1.61)	
Hispanic	1.49 (0.64–3.49)	
Other	Reference	
Era of diagnosis (N = 741)		0.93
1990–1999	1.02 (0.65–1.47)	
2000–2010	Reference	
Congestive heart failure (n = 740)	0.84 (0.53–1.31)	0.44
Family history		
Cardiomyopathy (n = 454)	0.79 (0.39–1.60)	0.51
Sudden death (n = 462)	0.62 (0.19–2.03)	0.43
LV dimension		
EDD (N = 741)		
z-score*	0.78 (0.70–0.87)	<0.001
Tertile		<0.001
<4.29	2.67 (1.58–4.50)	
4.29 to <6.29	1.56 (0.89–2.76)	
≥6.29	Reference	
ESD (n = 667)		
z-score	0.78 (0.70–0.87)	<0.001
Tertile		<0.001
<6.26	3.48 (1.98–6.12)	
6.26 to <8.17	1.59 (0.85–3.00)	
≥8.17	Reference	
LVFS (n = 700)		
z-score	1.08 (1.00–1.17)	0.041
Tertile		0.31
<−11.1	0.72 (0.44–1.19)	
−11.1 to <−8.99	0.73 (0.44–1.18)	
≥−8.99	Reference	
LVWT *z*-score		
Posterior (n = 576)	1.04 (0.96–1.12)	0.37
Septal (n = 536)	1.04 (0.94–1.16)	0.42
LV mass (n = 576)		
z-score	0.90 (0.83–0.98)	0.019
Tertile		0.23
<2.04	1.57 (0.90–2.74)	
2.04 to <4.00	1.50 (0.87–2.61)	
≥ 4.00	Reference	
PWT:EDD ratio (n = 576)		
Log (PWT:EDD ratio)	2.09 (1.24–3.53)	0.006
Tertile		0.009
<−2.30	0.40 (0.22–0.72)	
−2.30 to <−2.04	0.79 (0.49–1.29)	
≥−2.04	Reference	

Continued in the next column

Table 4 Continued

*Age at diagnosis and EDD *z*-score at diagnosis composed the final multivariate model for time to echo normalization (both terms, $p < 0.001$).
Abbreviations as in Table 2.

persistently abnormal. As a worst-case scenario with regard to misclassification, we reclassified these 156 children (32 + 124) as having normalized by 2 years after diagnosis, resulting in 317 with death/heart transplantation, 252 with normalization, and 172 with persistently abnormal echocardiograms. We obtained nearly the same multivariate model: it included age at diagnosis (HR: 0.90; 95% CI: 0.86 to 0.94; $p < 0.001$) and LVESD *z*-score (HR: 0.73; 95% CI: 0.65 to 0.81; $p < 0.001$).

Medical therapy. Only the presence or absence of anticongestive medication use was collected throughout the study period. The proportion of children receiving anticongestive medications at the time of diagnosis did not differ between groups: 85 of 96 (89%) in the normalized group, 284 of 317 (90%) in the death/transplantation group, and 293 of 328 (89%) in the persistently abnormal group. However, the proportion of children on anticongestive therapy at the time of the last echocardiogram within 2 years did differ significantly between groups ($p < 0.001$), with the highest usage in the death/heart transplantation group (210 of 213 [99%] vs. 83/96 [87%] in the normalized group and 284 of 328 [87%] in the persistently abnormal group).

Discussion

We report the 2-year cumulative incidence of recovery of normal LV size and function in children with idiopathic DCM from a large multicenter pediatric cardiomyopathy registry. Although half of the nearly 800 children died or underwent heart transplantation within 2 years of presentation, 9% did recover normal LV size and function by 1 year and 22% by 2 years, with a median time to normalization of 9 months. Younger age and less LV dilation at diagnosis independently predicted normalization within 2 years of presentation. However, 9% of the children who recovered normal echocardiographic function within 2 years later died or underwent heart transplantation.

Several studies have reported improved cardiac function in some children with DCM. The incidence of cardiac improvement ranges from 16% to 63%, depending on the definition of *improvement* and the cause of DCM (3,16–19). In a prospective multicenter carvedilol trial in children with heart failure, of 93 children with DCM, 59 (63%) had better New York Heart Association class or Ross heart failure stage at 6-month follow-up (16).

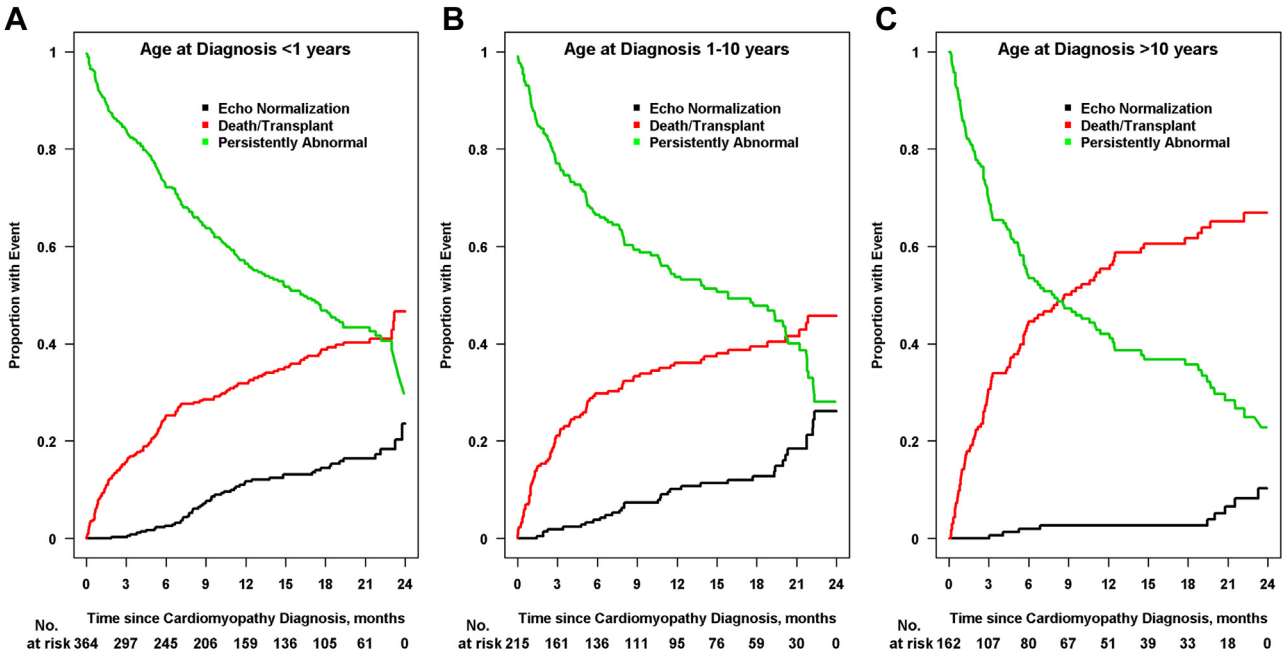

Figure 3 **Cumulative Incidence of Echocardiographic Normalization in Children With Idiopathic DCM (N = 741), by Age at Diagnosis**

Estimated cumulative incidence rates of recovery of normal echocardiographic function and size was similar in the 2 younger age groups (24% for those diagnosed before age 1 year **[A]** and 26% in those diagnosed before between ages 1 and 10 years **[B]**) and was lowest in children diagnosed after age 10 years (10% by age 2 years **[C]**). **Black lines** indicate echocardiographic normalization; **red lines** indicate death or transplantation; **green lines** indicate persistently abnormal findings on echocardiography.

Not surprisingly, our rate of *cardiac improvement,* defined as normal LV size and function by echocardiographic assessment, was lower than that in studies defining *cardiac improvement* as the resolution of heart failure symptoms. In an earlier single-center retrospective series by Lewis et al. (3), of 63 children with idiopathic DCM, 25% had normal LV function at follow-up. That study was similar to ours in that children with myocarditis and other known causes of DCM were excluded; all included patients had both depressed LV function and LV dilation at presentation, and the endpoint was recovery of LV function by echocardiographic measurement. In a recent report from the Australian National Population–based Study of Childhood Cardiomyopathy (20), the incidence of recovering normal echocardiographic LV function and size in children with DCM due to a variety of causes was 33% at 15 years. Although both of the aforementioned studies showed higher rates of normalization, this difference may have been due to the longer durations of follow-up (mean: 7 and 15 years [3,20]). Additionally, when those with a known cause for DCM are excluded, the rate of echocardiographic normalization in the Australian cohort is consistent with our finding, with normalization occurring in approximately 20% at 2 years among the 27 children with idiopathic DCM (20).

Younger age at diagnosis, specifically prior to age 10 years, predicted recovery of normal echocardiographic function and size within 2 years of presentation. Younger age has predicted cardiac recovery in other studies of pediatric DCM as well. Lewis et al. (3) found that children who recovered normal function were younger than those with persistently abnormal function (age: 2.1 ± 1.8 years vs. 4.5 ± 5.9 years).

Less LV dilation at presentation was the other independent predictor of recovering normal LV size and function within 2 years of presentation. Although at diagnosis our normalized group had a mean LVEDD *z*-score that was closer to normal than those of the other groups, the LV was, nonetheless, markedly dilated at presentation, with a mean *z*-score of 4.56 (1.87). Previously reported single-center series have had relatively small numbers of patients and have not found any echo parameters at presentation predictive of recovery, which may have been due to limited power (3,18). Our analysis contributes new information.

A previous PCMR report found that a higher LVEDD *z*-score at diagnosis was associated with transplantation but not with mortality in DCM from all causes (7). Knowing that heart transplantation affects the natural history of idiopathic DCM and competing outcomes, our finding of normal LV size and function in 22% of children by 2 years draws attention to the possibility for myocardial recovery even in children with marked LV dilation at presentation. Nonetheless, longer follow-up is necessary because some of these children (n = 9) later died or underwent heart transplantation for recurrent heart failure.

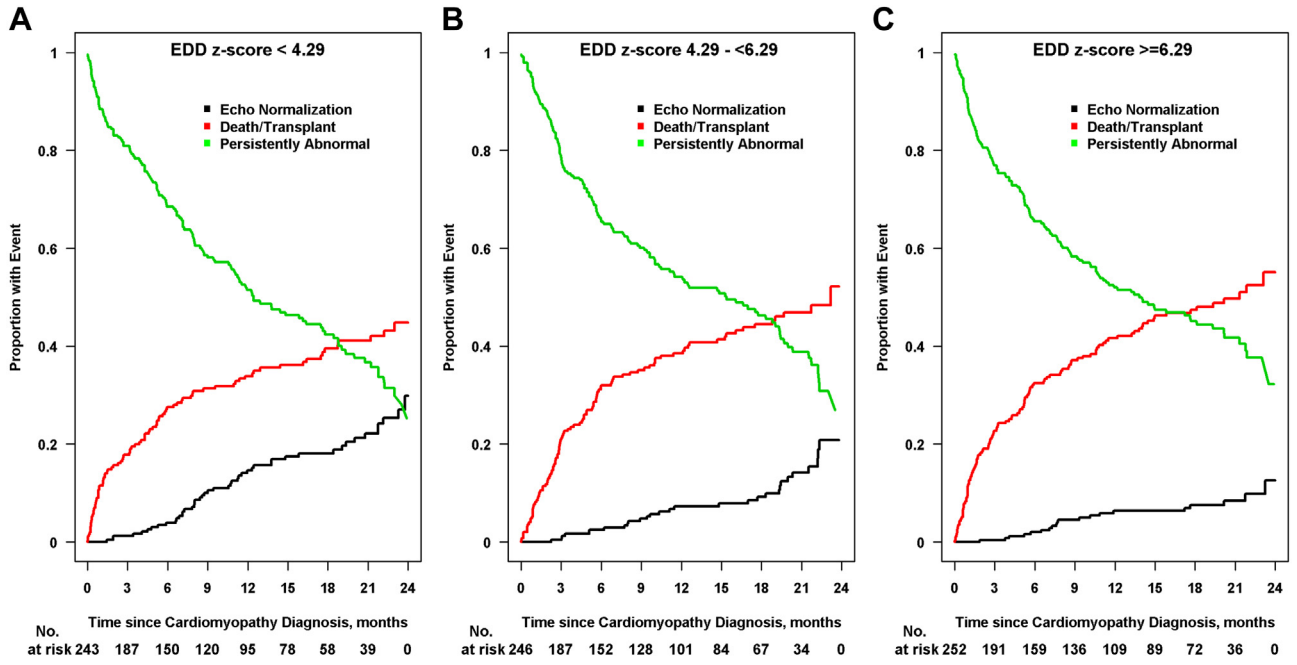

Figure 4 **Cumulative Incidence of Echocardiographic Normalization in Children With Idiopathic DCM (N = 741), by EDD *z*-Score Tertile From the Time of Diagnosis**

Children with lower end-diastolic dimension (EDD) *z*-scores at diagnosis were more likely to have recovered normal cardiac function by age 2 years (30% in those with EDD *z*-scores <4.29 **[A]**; 21% in those with scores in the middle tertile **[B]**; and 13% in those with scores ≥6.29 **[C]**). **Black lines** indicate echocardiographic normalization; **red lines** indicate death or transplantation; **green lines** indicate persistently abnormal findings on echocardiography.

This analysis was not designed to address the need for long-term follow-up or continued medical therapy in children recovering LV size and function. Most of these children were still receiving anticongestive medications at the time of the follow-up echocardiogram. The impact of the withdrawal of these medications on outcome could not be ascertained from this observational dataset.

An area of study is to identify children with full cardiac recovery in terms of normal diastolic function, normal cardiac magnetic resonance imaging results without residual inflammation or fibrosis, absence of an arrhythmogenic substrate, and normal LV size and function. In our study, some of the children with normal LV size and function at follow-up did later undergo heart transplantation, and 10 of 51 normalized cases that had follow-up data past 2 years had later abnormal LV size or function without recurring normalization. In the Australian report, none of those with normal LV size and function at follow-up had subsequent decreased function, death, or transplantation (20). Thus, the question remains as to who requires ongoing follow-up or medical therapy. Are these children at risk for recurrent heart failure, or is it only a subset of children at risk who have persistent abnormalities? How much change over time in LV size and function is natural variation or is due to a change in ventricular loading or geometry with alterations in medical therapy? Understanding this cardiac recovery versus remission further and predicting the impact of genotypic or genetic modifiers on prognosis, response to medical therapy, and response to ventricular assist support in children with the potential for cardiac recovery are key goals of future research.

Study limitations. The strength of the PCMR was the collaboration of 98 pediatric cardiac centers across the United States and Canada to collect data on children with DCM over 20 years. Importantly, serial echocardiograms collected during this observational study made this analysis possible. Nonetheless, the lack of standardized follow-up and time at which echocardiograms were obtained was a limitation. The echocardiographic data collected were abstracted annually, recording the latest echocardiographic findings from each year. Thus, the timing was left-censored, with some children classified as having a normal echocardiogram at 2-year follow-up, but the normalization could have occurred earlier, and the time-to-recovery values in this report may have been overestimates. However, our sensitivity analysis indicated that our findings were robust to reclassification of patients who had additional follow-up data, and in practice, many patients may not undergo echocardiograms more than annually.

Another limitation was that 15% of subjects known to have had abnormal LV function and dilation at diagnosis were excluded from analysis due to insufficient follow-up information. We found that these 127 patients were

slightly older at diagnosis than were the 741 analyzed. Therefore, because younger age at diagnosis was associated with earlier time to echo normalization, our reported recovery rates may have been mildly overestimated with respect to true rates in the pediatric idiopathic DCM population.

Information on the presence of tricuspid or mitral regurgitation and family history of sudden death or heart disease was available in only a few children, so these variables could not be included as candidate predictors in the multivariate model. Lastly, information related to medication use, such as beta-blockers and angiotensin-converting enzyme inhibitors, was insufficient for analysis of the association between medical therapy and recovery of normal echocardiographic function; or between discontinuation of therapy and outcome.

Conclusions

Despite marked LV dilation at presentation, 22% of children with idiopathic DCM recovered normal LV size and function within 2 years. Younger age and less LV dilation at diagnosis independently predicted normalization within 2 years of presentation. This improvement in cardiac function and size was not sustained in all children, which suggests that other indicators of cardiac recovery need to be explored, that longer follow-up may be required for some children, or that medical therapy may need to be continued beyond the recovery of normal LV size and function. Investigations related to predictors of cardiac recovery, such as genetic associations and outcomes, markers for cardiac recovery versus remission, and the impact of long-term medical therapy or ventricular unloading with ventricular assist devices in children with idiopathic DCM are important next steps.

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