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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Cardiomyopathies in children and adolescents: aetiology, management, and outcomes in the European Society of Cardiology EURObservational Research Programme Cardiomyopathy and Myocarditis Registry

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Abstract

Background and Aims Childhood-onset cardiomyopathies are rare and poorly characterized. This study examined the baseline characteristics and 1-year follow-up of children with cardiomyopathy in the first European Cardiomyopathy Registry.

Methods Prospective data were collected on individuals aged 1–<18 years enrolled in the European Society of Cardiology EURObservational Research Programme Cardiomyopathy and Myocarditis long-term registry (June 2014–December 2016).

Results A total of 633 individuals aged ≤18 years with hypertrophic [HCM; $n = 388$ (61.3%)], dilated [DCM; $n = 206$ (32.5%)], restrictive [RCM; $n = 28$ (4.4%)], and arrhythmogenic right ventricular cardiomyopathy [ARVC; $n = 11$ (1.7%)] were enrolled by 23 referral centres in 14 countries. Median age at diagnosis was 4.0 [interquartile range (IQR) 0–10] years, and there was a

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male predominance [$n = 372$ (58.8%)] across all subtypes, with the exception of DCM diagnosed <10 years of age; 621 (98.1%) patients were receiving cardiac medication and 80 (12.6%) had an implantable cardioverter-defibrillator. A total of 253 patients (253/535, 47.3%) had familial disease. Genetic testing was performed in 414 (67.8%) patients with a pathogenic or likely pathogenic variant reported in 250 (60.4%). Rare disease phenocopies were reported in 177 patients (28.0%) and were most frequent in patients under 10 years [142 (30.9%) vs. 35 (19.6%); $P = .003$]. Over a median follow-up of 12.5 months (IQR 11.3–15.3 months), 18 patients (3.3%) died [HCM $n = 9$ (2.6%), DCM $n = 5$ (3.0%), RCM $n = 4$ (16.0%)]. Heart failure events were most frequent in RCM patients (36.0%).

Conclusions The findings confirm the heterogeneous aetiology of childhood cardiomyopathies and show a high frequency of familial disease. Outcomes differed by cardiomyopathy subtype, highlighting a need for disease-specific evaluation and treatment.

Structured Graphical Abstract

Key Question

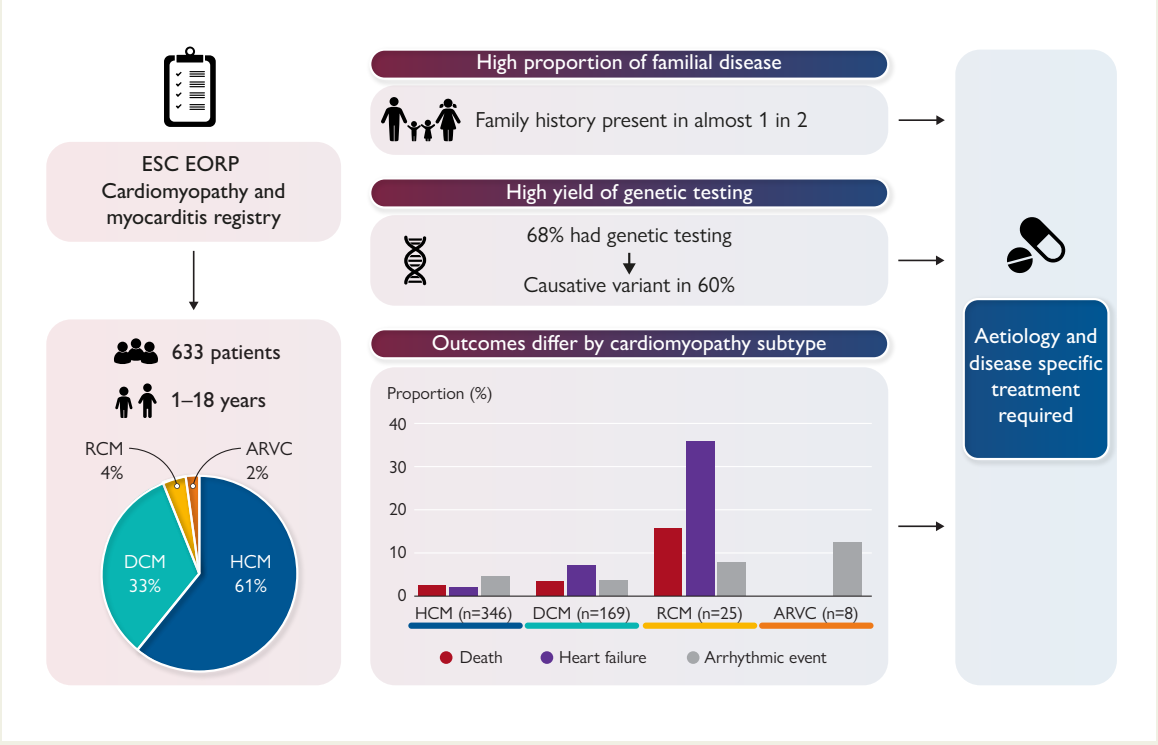
What are the characteristics of paediatric onset cardiomyopathy in a European population?

Key Finding

Among 633 individuals enrolled in the ESC EORP Cardiomyopathy and Myocarditis long-term registry, 47% had familial disease. Genetic testing identified a likely pathogenic variant in 60%. Outcomes differed by cardiomyopathy subtype. Patients with restrictive cardiomyopathy were at the highest risk of adverse cardiovascular events.

Take Home Message

The findings confirm the heterogeneous aetiology of childhood cardiomyopathies and show a high frequency of familial and genetic disease. Outcomes differed by cardiomyopathy subtype, highlighting a need for disease-specific evaluation and treatment.



Characteristics and outcomes of paediatric onset cardiomyopathy in a European population. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy.

Keywords Cardiomyopathy • Child • Registry • Genetics • Paediatric

Introduction

Cardiomyopathies are a heterogeneous group of diseases characterized by structural and functional abnormalities of the myocardium that are unexplained by abnormal loading conditions. They affect individuals of all ages,[1] but childhood-onset cardiomyopathies are rare (annual incidence 1.3 per 100 000) and poorly characterized.[2–8]

The EURObservational Research Programme (EORP) was launched by the European Society of Cardiology (ESC) in 2009 with the aim of describing the management and outcomes of specific cardiovascular diseases using robust observational methodologies. The EORP Cardiomyopathy and Myocarditis Registry has provided novel information on contemporary assessment and management of adult cardiomyopathies across Europe.[9,10] As part of the long-term phase of the

registry, recruitment was extended to include children and adolescents aged 1–18 years. This report summarizes the characteristics of the paediatric cohort with a particular focus on aetiology and short-term outcomes.

Methods

General registry design

The ESC EORP Cardiomyopathy and Myocarditis Registry is a prospective, multicentre observational registry of patients with a diagnosis of cardiomyopathy or myocarditis who were consecutively assessed at cardiology centres across Europe; detailed methodology for the pilot and adult long-term phases has been described.[9,10] Children and adolescents were recruited into the long-term registry between June 2014 and December 2016. The paediatric component of the registry was established in partnership with the Association for European Paediatric and Congenital Cardiology (AEPC) and included centres involved in the adult pilot and long-term phases that also managed children with cardiomyopathies as well as additional paediatric cardiology centres fulfilling pre-specified criteria (see Supplementary data online, *Methods*).[9] Written informed consent was obtained from all participants or their parents/guardians prior to enrolment, and the study received local ethical approval in accordance with each participating centre's governance requirements. The registry was managed by the ESC EORP and overseen by an executive committee.

Patient population

Cardiomyopathies were defined as myocardial disorders characterized by structural or functional abnormalities in the absence of coronary artery disease, hypertension, valve disease, or congenital heart disease (CHD) sufficient to cause the observed degree of myocardial abnormality.[1] The four major cardiomyopathy subtypes eligible for inclusion in the registry were hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM). Left ventricular non-compaction (LVNC) was reported as an associated clinical feature in each of the four cardiomyopathy subtypes. Genetic and non-genetic forms of cardiomyopathy were eligible for inclusion. For the paediatric subsection of the registry, inclusion criteria were (i) age at enrolment > 1 year and ≤18 years, (ii) ability to provide informed consent if over 16 years or via a parent or legal guardian if under 16 years, (iii) ability to comply with all study requirements, and (iv) fulfilment of conventional cardiomyopathy diagnostic criteria for probands or relatives, as previously described.[9,10] Patients with infantile-onset disease (diagnosed ≤1 year of age) were excluded from this registry during the design phase.[11–13]

Cardiovascular outcomes were ascertained by the treating cardiologist at each centre and defined *a priori* as the following:

(1) Major arrhythmic event: sudden cardiac death or resuscitated ventricular fibrillation (VF)/cardiac arrest or sustained ventricular tachycardia (VT)
(2) Major heart failure event: heart failure death, heart transplant, or ventricular assist device (VAD) implantation
(3) Major adverse cardiovascular events (MACE): any type of cardiovascular death or hospital urgent admission for cardiac reason

Among the 633 patients at baseline, only 620 patients are in the final database (as 13 patients were enrolled in sites non-compliant with European Community regulatory agreements and were therefore removed in transfer after lock of initial database). This study complies with the Declaration of Helsinki.

Statistical analyses

Continuous variables were reported as mean ± standard deviation and/or as median and interquartile range (IQR) when appropriate. Categorical variables were reported as percentages. Between-group comparisons were made using a non-parametric test (Kruskal–Wallis) or a χ^2 test or a Fisher's exact test if any expected cell count was <5. Disease presenting in early childhood (1–<10 years) was compared with that seen in later childhood using *a priori* determined age cut-offs of 10–18 years. Follow-up time for each patient was calculated from the date of enrolment into the registry. Cox proportional hazards model was used for survival estimates of combined endpoints reporting hazard ratios (HR) and 95% confidence intervals (CI). All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-sided *P* value of <.05 was considered as statistically significant.

Results

Enrolment and geographical distribution of participants

Twenty-three centres from 14 countries participated in the registry (see Supplementary data online, *Figure S1*). As of 31 December 2019, the total number of patients recruited and with locked data sets was 633. Over 75% of patients came from one of the three countries (Italy, UK, and France); 251 patients (39.7%) were from Southern Europe, 205 (32.4%) from Northern Europe, 106 (16.7%) from Western Europe, and 57 (9.0%) from Eastern Europe [defined according to United Nations geoscheme for Europe (https://unstats.un.org/unsd/methodology/m49/)]. In addition, nine patients were recruited from Egypt and five from Nigeria. Overall, 541 patients (86.7%) were probands and 83 were relatives (13.3%); in 9 patients, the proband status was unknown. A total of 193 patients (30.5%) were new cases, and 440 (69.5%) were under follow-up; 359 patients (56.7%) were recruited from an outpatient setting, and 274 (43.3%) were inpatients. Geographical differences in evaluation and management are summarized in Supplementary data online, *Table S1*. Patients from Eastern Europe were older at diagnosis and more likely to be inpatients and incident cases; they were also less likely to have rare disease phenocopies and to have undergone implantable cardioverter-defibrillator (ICD) implantation.

Cardiomyopathy subtypes and baseline characteristics

Hypertrophic cardiomyopathy was the commonest subtype [*n* = 388 (61.3%)], followed by DCM [*n* = 206 (32.5%)], RCM [*n* = 28 (4.4%)], and ARVC [*n* = 11 (1.7%)]; there was a statistically significant difference in the proportions of cardiomyopathy subtypes in the 1–<10 group compared with the 10–18 group, with a higher proportion of HCM and ARVC and a lower proportion of DCM and RCM (*P* < .001). Left ventricular non-compaction was reported in 86 patients (13.8% of those with available data) and was most frequent in those diagnosed aged 1–<10 years [*n* = 70 (15.8%) vs. *n* = 16 (9.0%) in those 10–18 years; *P* = .026]. Dilated cardiomyopathy was the commonest cardiomyopathy subtype associated with LVNC in the 1–<10 year group [*n* = 55 (35.5%) vs. HCM (*n* = 11, 4.2%) and RCM (*n* = 4, 15.4%); *P* < .001].

The baseline characteristics of the study cohort are shown in *Table 1*. The median age at diagnosis for the whole cohort was 4 (0, 10) years, and there was a male predominance across all cardiomyopathy subtypes, with the exception of DCM diagnosed aged 1–<10 years of age.

The most common reason for diagnosis across the whole cohort was symptoms [*n* = 191 (30.8%)], followed by family screening [*n* = 139 (22.4%)], incidental finding [*n* = 133 (21.5%)], and cardiac arrest [*n* = 17 (2.7%)]. Across all age groups, patients with DCM and RCM were most commonly diagnosed due to symptoms, whereas family

Table 1 Baseline characteristics for each cardiomyopathy subtype stratified by age group (1–<10 vs. 10–18 years)

	Total (*N* = 633)	*P* value < 10 vs. 10–18	1–<10 years					10–18 years				
			All (*N* = 452)	HCM (*N* = 267)	DCM (*N* = 157)	RCM (*N* = 26)	ARVC (*N* = 2)	All (*N* = 179)	HCM (*N* = 120)	DCM (*N* = 48)	RCM (*N* = 2)	ARVC (*N* = 9)
Index case	541/624 (86.7%)	.865	388/447 (86.8%)	220/266 (82.7%)	144/153 (94.1%)	22/26 (84.6%)	2/2 (100.0%)	151/175 (86.3%)	100/120 (83.3%)	41/44 (93.2%)	2/2 (100.0%)	8/9 (88.9%)
Age at enrolment (years) *Median (Q1,Q3)*	9.0 (4, 14)	<.001	6.5 (3, 10)	7.0 (3, 11)	5.0 (2, 9)	5.5 (3, 8)	12 (10, 14)	14.0 (13, 15)	14.0 (13, 15)	14.0 (13, 15)	15.5 (15, 16)	14.0 (13, 15)
Age at diagnosis (years) *Median (Q1,Q3)*	4 (0, 10)	<.001	1.0 (0, 5)	1.0 (0, 5)	0.0 (0, 3)	3.0 (1, 6)	5.0 (1, 9)	13.0 (11, 14)	13.0 (11, 14)	12.0 (11, 14)	14.5 (14, 15)	14.0 (11, 15)
Male	372/633 (58.8%)	.080	256/452 (56.6%)	167/267 (62.5%)	72/157 (45.9%)	16/26 (61.5%)	1/2 (50.0%)	115/179 (64.2%)	76/120 (63.3%)	32/48 (66.7%)	1/2 (50.0%)	6/9 (66.7%)
Familial disease	253/535 (47.3%)	.530	117/382 (46.3%)	116/230 (50.4%)	52/127 (40.9%)	8/23 (34.8%)	1/2 (50.0%)	75/152 (49.3%)	57/104 (54.8%)	12/37 (32.4%)	2.2 (100.0%)	4/9 (44.4%)
Presence of symptoms	332/633 (52.4%)	.583	234/452 (51.8%)	106/267 (39.7%)	109/157 (69.4%)	18/26 (69.2%)	1/2 (50.0%)	97/179 (54.2%)	54/120 (45.0%)	36/48 (75.0%)	2/2 (100.0%)	5/9 (55.6%)
Vagal or non-cardiac syncope	23/325 (7.1%)	<.001	11/227 (4.8%)	6/103 (5.8%)	4/105 (3.8%)	1/18 (5.6%)	0/1 (0.0%)	12/97 (12.4%)	8/54 (14.8%)	3/36 (8.3%)	1/2 (50.0%)	0/5 (0.0%)
Suspected arrhythmic/ cardiogenic syncope	28/325 (8.6%)		8/227 (3.5%)	6/103 (5.8%)	2/105 (1.9%)	0/18 (0.0%)	0/1 (0.0%)	20/97 (20.6%)	11/54 (20.4%)	5/36 (13.9%)	0/2 (0.0%)	4/5 (80.0%)
Syncope of uncertain mechanism	13/325 (4.0%)		9/227 (4.0%)	8/103 (7.8%)	0/105 (0.0%)	1/18 (5.6%)	0/1 (0.0%)	4/97 (4.1%)	3/54 (5.6%)	1/36 (2.8%)	0/2 (0.0%)	0/5 (0.0%)
Chest pain	34/332 (10.2%)	.001	16/234 (6.8%)	12/106 (11.3%)	2/109 (1.8%)	2/18 (11.1%)	0/1 (0.0%)	18/97 (18.6%)	16/54 (29.6%)	2/36 (5.6%)	0/2 (0.0%)	0/5 (0.0%)
NYHA/Ross I	119/278 (42.8%)	.509	88/193 (45.6%)	35/91 (38.5%)	48/86 (55.8%)	4/15 (26.7%)	1/1 (100.0%)	31/85 (36.5%)	26/51 (51.0%)	2/28 (7.1%)	0/2 (0.0%)	3/4 (75.0%)
NYHA/Ross II	112/278 (40.3%)		74/193 (38.3%)	46/91 (50.5%)	22/86 (25.6%)	6/15 (40.0%)	0/1 (0.0%)	38/85 (44.7%)	21/51 (41.2%)	17/28 (60.7%)	0/2 (0.0%)	0/4 (0.0%)
NYHA/Ross III	36/278 (12.9%)		23/193 (11.9%)	9/91 (9.9%)	10/86 (11.6%)	4/15 (26.7%)	0/1 (0.0%)	13/85 (15.3%)	3/51 (5.9%)	7/28 (25.0%)	2/2 (100.0%)	1/4 (25.0%)
NYHA/Ross IV	11/278 (4.0%)		8/193 (4.1%)	1/91 (1.1%)	6/86 (7.0%)	1/15 (6.7%)	0/1 (0.0%)	3/85 (3.5%)	1/51 (2.0%)	2/28 (7.1%)	0/2 (0.0%)	0/4 (0.0%)
Extreme lethargy	39/332 (11.7%)	.872	28/234 (12.0%)	12/106 (11.3%)	13/109 (11.9%)	3/18 (16.7%)	0/1 (0.0%)	11/97 (11.3%)	3/54 (5.6%)	6/36 (16.7%)	2/2 (100.0%)	0/5 (0.0%)
Palpitations	61/332 (18.4%)	<.001	25/234 (10.7%)	19/106 (17.9%)	4/109 (3.7%)	2/18 (11.1%)	0/1 (0.0%)	36/97 (37.1%)	22/54 (40.7%)	11/36 (30.6%)	2/2 (100.0%)	1/5 (20.0%)
Failure to thrive	76/332 (22.9%)	<.001	66/234 (28.2%)	27/106 (25.5%)	32/109 (29.4%)	7/18 (38.9%)	0/1 (0.0%)	10/97 (10.3%)	4/54 (7.4%)	6/36 (16.7%)	0/2 (0.0%)	0/5 (0.0%)

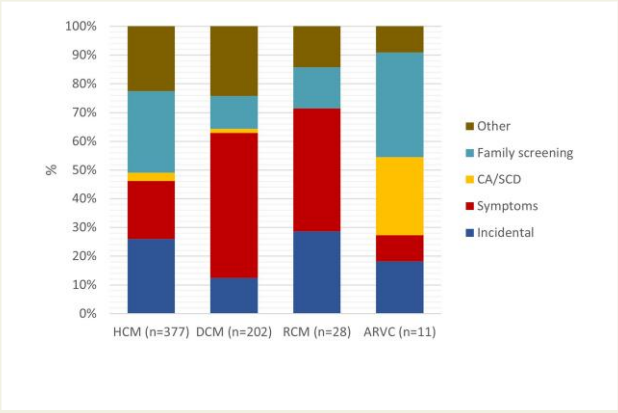


Figure 1 Reasons for diagnosis for each cardiomyopathy subtype. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; CA/SCD, cardiac arrest/sudden cardiac death

screening was the most common reason for diagnosis in HCM and ARVC (*Figure 1*).

Clinical characteristics

Symptoms were reported in 332 patients (52.4%) and were most common in patients with DCM and RCM (*Table 1*).

A history of atrial fibrillation and transient ischaemic attack/stroke was rare [eight (1.3%) and six (1.0%) patients, respectively]. Ventricular arrhythmia prior to enrolment was reported in 51 patients (8.1%): 27 had a history of sustained VT, which was more common in patients aged 10–18 years [15 out of 179 patients (8.4%) compared with 12 out of 452 (2.7%) in those diagnosed aged 1–< 10 years of age ($P = .001$)], and 24 patients had suffered a resuscitated VF cardiac arrest (no difference between age groups). There was a non-significant trend towards an increased frequency of ventricular arrhythmia in older patients with ARVC.

Co-existing CHD was documented in 103 patients (16.5%), including atrial septal defects ($n = 36$, 5.8%) and ventricular septal defects ($n = 22$, 3.5%). The frequency of congenital heart lesions other than atrial septal defect and ventricular septal defect was higher in those diagnosed aged 1–<10 years of age [$n = 42$ (9.4%) vs. 3 (1.7%) in the 10–18 year group, $P < .001$].

Genetic testing and aetiology

Familial disease was reported in 253 patients ($n = 253/535$, 47.3%); in those diagnosed between 10–18 years, familial disease was most frequent in HCM and least frequent in DCM [$n = 57$ (54.8%) vs. $n = 12$ (32.4%), $P = .046$]. Similar trends were observed in the 1–<10 year group (see Supplementary data online, *Figure S2*).

Genetic testing was performed in 414 patients (67.8%). In those diagnosed 1–<10 years, genetic testing was most frequent in ARVC [2 (100.0%)], followed by HCM [191 (74.9%)], RCM [18 (72.0%)], and DCM [90 (59.6%); $P = .008$] for global comparison; in those aged 10–18, genetic testing was most frequent in ARVC [$n = 8$ (88.9%)] followed by HCM [$n = 81$ (69.2%)], RCM [$n = 1$ (50.0%)], and DCM [$n = 22$ (45.8%); $P = .007$]. A causative variant was documented in 250 patients (60.4%), with a higher yield from testing in those aged 10–18 years [$n = 77$ (68.8%) vs. $n = 172$ (57.1%) compared with those aged 1–<10 years; $P = .032$]. In those aged 1–<10 years, the prevalence of reported causative variants was highest in HCM [128 (67.0%) vs. 10 (55.6%) in RCM, 1 (50.0%) in ARVC, and 33 (36.7%) in DCM; $P < .001$]; in those 10–18 years, there was no difference in prevalence of reported causative variants between cardiomyopathy subtypes (see Supplementary data online, *Figure S3*). *Table 2* and Supplementary data online, *Table S2*, describe the disease-causing variants identified on genetic testing by age and diagnosis. Variants were most commonly identified in sarcomeric protein genes for all cardiomyopathy subtypes except ARVC.

Phenocopies were reported in 177 patients (28.0%) (*Figure 2*): malformation syndromes [$n = 75$ (11.8%)], neuromuscular disorders [$n = 49$ (7.7%)], inborn errors of metabolism [$n = 20$ (3.2%)], mitochondrial disorders [$n = 18$ (2.8%)], and chromosomal abnormalities [$n = 15$ (2.4%)]. Phenocopies were most frequent in patients aged 1–<10 years [142 (30.9%) vs. 35 (19.6%) in those aged 10–18 years; $P = .003$], particularly in younger HCM patients [$n = 116$ (43.4%); $P < .001$ vs. other subtypes] and older DCM patients [$n = 18$ (37.5%); $P = .002$ vs. other subtypes]. Data on specific rare disease phenocopies are reported in the Supplementary data online, *Tables S3* and *S4*.

Specialized diagnostic tests

Supplementary data online, *Table S5*, shows the utilization of cardiac investigations at baseline. When performed, ambulatory ECG monitoring showed sinus rhythm throughout in the majority of patients, with paroxysmal atrial fibrillation identified in two patients (0.6%) and conduction disease in five (1.5%). Non-sustained VT (NSVT) was documented in 14 patients (4.1%), with the highest frequency in patients with DCM, although this did not reach statistical significance. A total of 193 patients (30.5%) underwent cardiac magnetic resonance imaging (MRI); the presence or absence of late gadolinium enhancement was assessed in 101 (59.1%) patients.

Treatment at baseline

A total of 621 patients (98.1%) were receiving one or more cardiovascular medications at the time of enrolment. The breakdown of medication class by cardiomyopathy subtype is shown in *Table 3*. The most commonly used drugs were beta-blockers ($n = 372$, 58.8%); angiotensin-converting enzyme (ACE) inhibitors were used in 158 children with DCM (77.1%). Eighteen patients (4.0%) were receiving oral anticoagulation, of whom 14 had DCM.

Follow-up and outcomes

Five hundred and forty-eight patients (88.4%) had 1-year follow-up data. Median follow-up was 12.5 months (IQR 11.3–15.3 months). Patients with follow-up were less likely to have heart failure symptoms at baseline but did not otherwise differ in baseline characteristics (see Supplementary data online, *Table S6*). By the end of follow-up, 80 (12.9%) had received an ICD, the majority of which was for primary prophylaxis (75.0%). Devices were most commonly implanted in older patients [10–18 years $n = 40$ (22.3%) vs. 1–<10 years $n = 40$ (8.9%), $P < .001$] and in those with ARVC ($n = 7$, 63.6%), followed by HCM ($n = 56$, 14.5%). Ten patients (1.6%) received a permanent pacemaker, and one patient had a cardiac resynchronization therapy device.

Twenty-six (4.2%) patients (15 with DCM) had a VAD, and 23 patients (3.7%) (14 with DCM) received a heart transplant. The number of patients with HCM who had undergone a septal myectomy was 41 (10.6%), and this was most frequent in younger patients [$n = 35$ (13.1%) vs. $n = 6$ (5.0%) in the 10–18 year group; $P = .016$].

Table 2 Disease-causing variant identified by genetic testing by age group (1–<10 vs. 10–18 years)

	Total 414	1–<10 years ($n = 301$)				10–18 years ($n = 112$)				*P* value 1–<10 vs. 10–18 years
		HCM ($n = 191$)	DCM ($n = 90$)	RCM ($n = 18$)	ARVC ($n = 2$)	HCM ($n = 81$)	DCM ($n = 22$)	RCM ($n = 1$)	ARVC ($n = 8$)	
Sarcomeric	139 (33.7%)	68 (35.6%)	17 (18.9%)	8 (44.4%)	0 (0.0%)	42 (51.9%)	3 (13.6%)	1 (100%)	0 (0.0%)	.06
Dystrophin	6 (1.4%)	0 (0.0%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	3 (13.6%)	0 (0.0%)	0 (0.0%)	.05
Z disc	5 (1.2%)	1 (0.5%)	1 (1.1%)	1 (5.6%)	0 (0.0%)	1 (1.2%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	.51
Nuclear envelope	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	>.999
Desmosomal	23(5.6%)	6 (3.1%)	6 (6.7%)	1 (5.6%)	1 (50.0%)	2 (2.5%)	1 (4.5%)	0 (0.0%)	6 (75.0%)	.18
Ion channel	4 (1.0%)	0 (0.0%)	2 (2.2%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	.58
RASopathy	31 (7.5%)	26 (13.6%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	4 (4.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	.06
Metabolic	9 (2.2%)	7 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	>.999
Mitochondrial	10 (2.4%)	5 (2.6%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	3 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	.73

Genetic testing was performed in 414 patients (67.8%). Genetic testing identified a causative variant in 250 (60.4%) patients and was negative in 250 (39.6%). In 22 patients, genetic testing status was unknown.

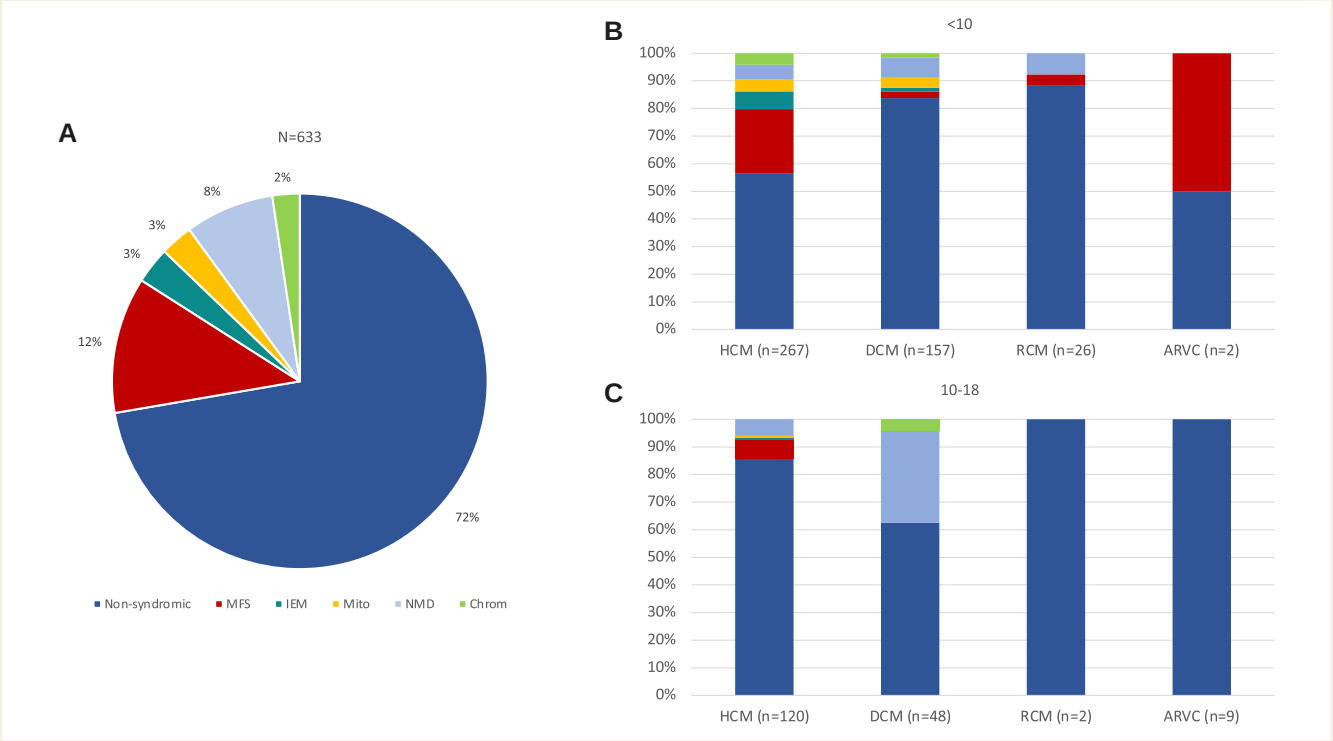


Figure 2 Frequency of rare disease causes in childhood cardiomyopathies. Proportion of rare disease causes across all age groups and cardiomyopathy subtypes. (*A*) Proportion of rare disease causes by cardiomyopathy subtype in patients diagnosed under 10 years of age. (*B*) Proportion of rare disease causes by cardiomyopathy subtype in patients diagnosed between 10 and 18 years of age. MFS, malformation syndrome; IEM, inborn error of metabolism; Mito, mitochondrial cytopathy; NMD, neuromuscular disorder; Chrom, chromosomal abnormality

Eighteen patients (3.3%) died [HCM $n = 9$ (2.6%), DCM $n = 5$ (3.0%). RCM $n = 4$ (16.0%)]. Cause of death was heart failure ($n = 8$), arrhythmia ($n = 1$), cerebrovascular accident ($n = 1$), systemic haemorrhage ($n = 2$), and other ($n = 6$). Cause of death by age and cardiomyopathy subtype is described in *Table 4*. Arrhythmic events occurred most commonly in patients with ARVC (12.5%) followed by RCM (8.0%). Heart failure events were most frequent in RCM patients (36.0%), followed by DCM (7.1%) (*Figure 3*). Compared with those with HCM, children with

Table 3 Medication utilization in each cardiomyopathy subtype by age group (<10 vs. 10–18 years)

	Total (*N* = 633)	*P* value < 10 vs. 10–18	1–<10 years					10–18 years				
			All (*N* = 452)	HCM (*N* = 267)	DCM (*N* = 157)	RCM (*N* = 26)	ARVC (*N* = 2)	All (*N* = 179)	HCM (*N* = 120)	DCM (*N* = 48)	RCM (*N* = 2)	ARVC (*N* = 9)
Beta-blockers	372/633 (58.8%)	.020	278/452 (61.5%)	157/267 (58.8%)	108/157 (68.8%)	12/26 (46.2%)	1/2 (50.0%)	92/179 (51.4%)	56/120 (46.7%)	30/48 (62.5%)	1/2 (50.0%)	5/9 (55.6%)
ACE inhibitors	191/633 (30.2%)	.128	144/452 (31.9%)	9/267 (3.4%)	121/157 (77.1%)	13/26 (50.0%)	1/2 (50.0%)	46/179 (25.7%)	6/120 (5.0%)	37/48 (77.1%)	0/2 (0.0%)	3/9 (33.3%)
Angiotensin II receptor blockers	6/633 (0.9%)	1.000	5/452 (1.1%)	0/267 (0.0%)	4/157 (2.5%)	1/26 (3.8%)	0/2 (0.0%)	1/179 (0.6%)	0/120 (0.0%)	1/48 (2.1%)	0/2 (0.0%)	0/9 (0.0%)
Diuretics	138/452 (30.5%)	.171	108/333 (32.4%)	28/169 (16.6%)	61/138 (44.2%)	18/25 (72.0%)	1/1 (100.0%)	30/117 (25.6%)	6/67 (9.0%)	22/44 (50.0%)	2/2 (100.0%)	0/4 (0.0%)
Mineralocorticoid receptor antagonists	120/633 (19.0%)	.993	86/452 (19.0%)	17/267 (6.4%)	57/157 (36.3%)	11/26 (42.3%)	1/2 (50.0%)	34/179 (19.0%)	7/120 (5.8%)	26/48 (54.2%)	1/2 (50.0%)	0/9 (0.0%)
Antiplatelet agents	63/633 (10.0%)	.581	47/452 (10.4%)	4/267 (1.5%)	27/157 (17.2%)	16/26 (61.5%)	0/2 (0.0%)	16/179 (8.9%)	4/120 (3.3%)	12/48 (25.0%)	0/2 (0.0%)	0/9 (0.0%)
Oral anticoagulants	18/453 (4.0%)	.271	11/333 (3.3%)	1/169 (0.6%)	9/138 (6.5%)	1/25 (4.0%)	0/1 (0.0%)	7/118 (5.9%)	1/67 (1.5%)	5/44 (11.4%)	1/2 (50.0%)	0/5 (0.0%)
Amiodarone	17/583 (2.9%)	.275	10/416 (2.4%)	8/256 (3.1%)	1/136 (0.7%)	1/22 (4.5%)	0/2 (0.0%)	7/165 (4.2%)	2/112 (1.8%)	4/43 (9.3%)	0/1 (0.0%)	1/9 (11.1%)
Disopyramide	17/583 (2.9%)	1.000	12/418 (2.9%)	11/259 (4.2%)	0/135 (0.0%)	1/22 (4.6%)	0/2 (0.0%)	5/163 (3.1%)	5/115 (4.3%)	0/39 (0.0%)	0/1 (0.0%)	0/8 (0.0%)
Digoxin	28/594 (4.7%)	.240	23/429 (5.4%)	0/248 (0.0%)	19/154 (12.3%)	4/25 (16.0%)	0/2 (0.0%)	5/163 (3.1%)	1/111 (0.9%)	3/42 (7.1%)	1/2 (50.0%)	0/8 (0.0%)
Calcium antagonists	14/633 (2.2%)	.237	8/452 (1.8%)	7/267 (2.6%)	1/157 (0.6%)	0/26 (0.0%)	0/2 (0.0%)	6/179 (3.4%)	4/120 (3.3%)	1/48 (2.1%)	1/2 (50.0%)	0/9 (0.0%)
Ivabradine	15/453 (3.3%)	.235	9/333 (2.7%)	1/169 (0.6%)	7/138 (5.1%)	1/25 (4.0%)	0/1 (0.0%)	6/118 (5.1%)	0/67 (0.0%)	6/44 (13.6%)	0/2 (0.0%)	0/5 (0.0%)

Table 4 Outcomes by cardiomyopathy subtype and age group (1–<10 vs. 10–18 years)

	Total ($n = 548$)	1–<10 years ($n = 392$)				10–18 years ($n = 154$)				*P* value 1–<10 years vs. 10–18 years
		HCM ($n = 234$)	DCM ($n = 132$)	RCM ($n = 24$)	ARVC ($n = 2$)	HCM ($n = 111$)	DCM ($n = 36$)	RCM ($n = 1$)	ARVC ($n = 6$)	
Death	18 (3.3%)	9 (3.8%)	3 (2.3%)	4 (16.7%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	.101
Heart failure	8 (1.5%)	2 (0.9%)	2 (1.5%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	
Arrhythmia	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CVA	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (.0%)	0 (0.0%)	0 (0.0%)	
Systemic haemorrhage	2 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	6 (1.1%)	5 (2.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Septal myectomy	41 (7.5%)	35 (13.1%)				6 (5.0%)				.016
Major heart failure event	28 (5.1%)	6 (2.6%)	7 (5.3%)	9 (37.5%)	0 (0.0%)	1 (0.9%)	5 (13.9%)	0 (0.0%)	0 (0.0%)	.413
Major arrhythmic event	25 (4.6%)	11 (4.7%)	3 (2.3%)	2 (8.3%)	0 (0.0%)	5 (4.5%)	3 (8.3%)	0 (0.0%)	1 (16.7%)	.375
Major cardiovascular event	66 (12.0%)	27 (11.6%)	8 (6.1%)	9 (37.5%)	0 (0.0%)	14 (12.6%)	6 (16.7%)	1 (100%)	1 (16.7%)	.339

RCM showed an increased risk of reaching the composite endpoint of major heart failure events [HR 27.34 (95% CI 9.72–76.94) $P < .001$], major arrhythmic event (HR 29.48 (95% CI 2.67–325.42), $P = .006$), and MACE (HR 6.47 (95% CI 3.13–13.35) $P < .001$). There was no difference in outcome by proband status.

Discussion

In this study from the first European paediatric cardiomyopathy registry, we demonstrate a high prevalence of familial and genetic disease, even in the youngest children, and a high symptom burden requiring medication, implantable devices, and surgical therapy. Patients with RCM were at the highest risk of adverse cardiovascular events (*Structured Graphical Abstract*).

Clinical characteristics of the cohort

In contrast with published paediatric registry data from North America[6] and Australia,[7] where DCM accounts for more than 50% of cardiomyopathies, HCM was the most frequent diagnosis in the registry. This difference may relate to the exclusion of patients diagnosed in the first year of life, who may have a higher incidence of DCM compared with HCM and other cardiomyopathy subtypes.[6,14] It is also possible that families with HCM were more likely to be referred, due to the perceived higher risk of genetic disease.[15–17] Nevertheless, as the majority of patients across all cardiomyopathy subtypes were index cases, it is also plausible that HCM may be more common in the paediatric population than previously assumed.

In keeping with previous adult and paediatric studies, there was a male predominance across all cardiomyopathy subtypes in all age groups, with the exception of DCM in patients diagnosed under 10 years of age. In adults, it is suggested that this may be related to modifier effects of sex hormones,[18] but the fact that this sex difference is present even in pre-adolescence suggests that other genetic and epigenetic factors are important.

Associated congenital disease

Associated CHD was seen in one-sixth of patients in this study and was particularly common in younger patients diagnosed with cardiomyopathies. The frequency of CHD in children with cardiomyopathies has not been evaluated systematically previously but in this study was substantially higher than the population prevalence of CHD, which is estimated at 0.8% in Europe.[19] This may reflect the higher prevalence of syndromic aetiologies (particularly RASopathies and chromosomal abnormalities) in the younger age group but could also suggest different genetic causes for cardiomyopathies in the very young.

Familial disease

A major finding in this study was the large proportion of patients with familial disease, which remained even after removal of relatives of an index patient. Although most frequent in patients with HCM, this was consistent across all cardiomyopathy subtypes and across all age groups. This finding corroborates reports from previous registry and consortium studies.[20,21] Furthermore, the overall yield of genetic testing was also high, exceeding 60% in HCM, ARVC, and RCM. Dilated cardiomyopathy had the lowest overall yield of genetic testing (41%), but this was higher for those aged 10–18 years (59.1%). The overall yield of genetic testing was higher than reported in the North American Pediatric Cardiomyopathy Registry (PCMR) (60% vs. 48%), but they found similar differences in the yield by cardiomyopathy type.[21] It is possible that this high yield reflects selection bias from expert centres with ready access to genetic testing; indeed, the proportion of patients undergoing genetic testing was higher in than in the PCMR data set (68% vs. 53%).[21] However, these findings suggest a genetic basis for disease should always be considered in children with cardiomyopathy. As in adults, the majority of disease-causing variants in children with HCM was in sarcomeric protein genes. On the

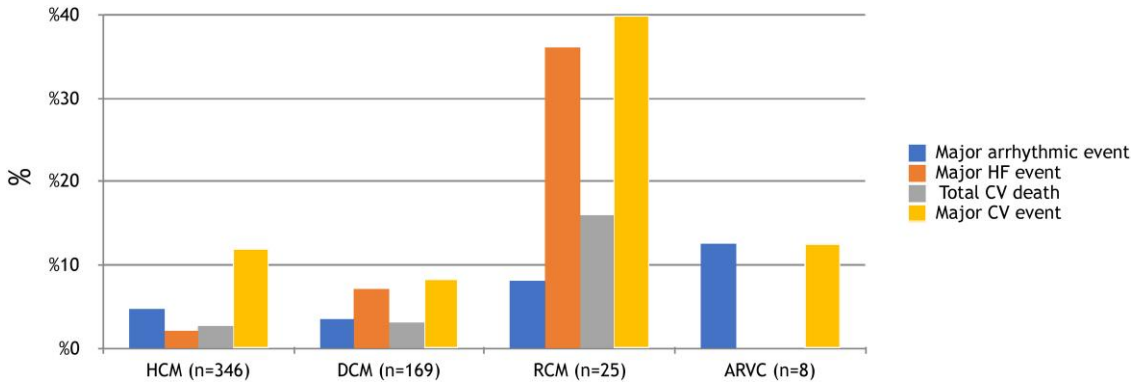


Figure 3 Rate of combined events at 1-year follow-up for each subtype of cardiomyopathy

other hand, the predominance of variants in sarcomere genes other than titin in DCM contrasts with adult cohorts.[15,16,22–24]

In keeping with previous studies in childhood, our data demonstrate a substantially higher frequency of rare disease phenocopies compared with adults, particularly in those diagnosed in the first decade of life. Malformation syndromes, particularly Noonan syndrome and related RAS-MAPK disorders, were most frequent among the rare disease phenocopies. These diagnoses are important to recognize as they are associated with different outcomes[8,12,25] and, increasingly, are amenable to targeted therapeutic approaches, including enzyme replacement therapy for some inborn errors of metabolism,[26] MEK inhibition for some patients with disorders of the RAS-MAPK developmental pathway (e.g. Noonan syndrome),[27] and genome editing in patients with Duchenne muscular dystrophy.[28]

Systematic evaluation

The use of comprehensive clinical diagnostic investigations in this population was high, reflecting the complexity of diagnosis in childhood cardiomyopathies and the characteristics of the enrolling centres. A relatively high proportion of patients underwent cardiac MRI and exercise testing, although the use of these tests is necessarily limited in the very young. In contrast, nearly half the patients enrolled had not undergone ambulatory ECG monitoring. Importantly, when this was performed, it led to the detection of NSVT in nearly 5% of patients, which could have implications for sudden cardiac death risk stratification, particularly in HCM.[29,30] Similarly, although echocardiography was performed in the vast majority of patients, an assessment of left atrial diameter was not recorded in nearly 40% of children with HCM. As left atrial size is an important predictor of ventricular arrhythmia risk in childhood HCM,[29,30] these data suggest a potential gap in existing recommendations for the investigation and management of paediatric cardiomyopathies.

Treatment

A high proportion of patients in this study were receiving cardiac medication. This could indicate a bias towards patients with more severe disease but may also reflect local clinical practice as medication may be prescribed as prophylactic therapy in some centres. Nearly 1 in 10 individuals received an ICD, most commonly for primary prophylaxis. The proportions of ICD implantation in patients with HCM were in keeping with previous studies.[31] In contrast, although the numbers were small, a substantial proportion (over 60%) of patients with ARVC had undergone ICD implantation, consistent with the findings from the adult EORP cardiomyopathy registry.[9] A small number of patients with HCM had undergone septal myectomy at the time of enrolment, and this was most frequent in those diagnosed aged 1–<10 years of age, most likely reflecting the increased prevalence of syndromic aetiologies in this age group, which have a higher prevalence of left ventricular outflow tract obstruction.[32]

Outcomes

Children with RCM had the worst short-term outcomes, but the frequency of adverse events differed by cardiomyopathy type; specifically, children with DCM were most likely to experience a heart failure event, whereas patients with HCM and ARVC more commonly experienced an arrhythmic event. The finding that patients with HCM had relatively good short-term outcomes is consistent with previous reports that, outside of infancy, children and adolescents have a low incidence of death and heart failure in childhood.[8,12,33] However, long-term morbidity associated with childhood diagnosis is considerable, with up to 50% experiencing adverse cardiac outcomes within 25 years.[20] One in 10 patients with HCM underwent septal myectomy during follow-up. Analysis was not performed for myectomy by centre/geographical region, but centre-specific differences in the management of left ventricular outflow tract obstruction are likely given the sparsity of evidence in paediatric disease. The lack of a difference in outcomes by age in this study, compared with previous reports, could be explained by the exclusion of infants, who are recognized to have a worse prognosis and higher mortality.[11,12,34]

In contrast to adult disease, the prevalence of atrial fibrillation and stroke in children with cardiomyopathy is extremely low. However, nearly 1 in 10 children had a history of sustained VT or VF at enrolment detected on ambulatory monitoring, interrogation of ICD download, or following presentation with a cardiac arrest. This was most common in patients with ARVC, although the numbers with this diagnosis were very small and may reflect a more severe end of the spectrum for this condition. Importantly, a history of sustained VT or VF was recorded in patients with all cardiomyopathy subtypes and age groups with the exception of RCM, highlighting the importance of considering sudden death risk in all childhood cardiomyopathies. The low burden of arrhythmia in RCM could be explained by small cohort size, as it is traditionally described to have a high, largely atrial, arrhythmic burden attributed to significant biatrial enlargement.[35,36] However, it could also suggest differing arrhythmogenic pathways in subtypes of paediatric cardiomyopathies.

Limitations

In common with other registry studies, the data in this study may not be fully representative of the general paediatric cardiomyopathy population, particularly given that over 75% of the data originate from expert centres in three European countries and that participation in the registry was voluntary with no data collected on individuals declining to participate. It is therefore beyond the scope of this study to determine the true incidence or natural history of these conditions in childhood. This also limits the ability to perform detailed geographical comparisons. The registry contains small numbers of patients with RCM and ARVC, and results should be interpreted with caution. For RCM, this may reflect different care pathways for these patients with different clinicians leading their care. For ARVC, it likely reflects the current paradigm that this disease uncommonly presents during childhood. The small numbers of patients and number of events also limit our statistical power; meaning analysis was largely descriptive and reported CI are wide. Patients under the age of 1 year were excluded from the registry by the ESC research committee during the design phase; given that obstetricians and neonatologists were not formally involved in the multinational EORP network, thereby, the consecutiveness and early identification of patients enrolled would not have been systematic. This group are recognized to have a higher proportion of syndromic disease and worse long-term outcomes.[11–13] This may have distorted the proportion of patients with each cardiomyopathy subtype as well as other baseline characteristics. There was no independent confirmation of the consecutiveness of the patients or verification of the imaging and clinical features.

Conclusions

This is the first European paediatric cardiomyopathy registry. The findings confirm the heterogeneous aetiology of childhood cardiomyopathies and show a high frequency of familial disease. Outcomes differed by cardiomyopathy subtype, highlighting a need for disease-specific evaluation and treatment.

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Supplementary data

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

Declarations

Disclosure of Interest

J.P.K. reports consultancy fees from Cytokinetics and Tenaya, outside the submitted work. L.T. reports personal fees from Servier and CVie Therapeutics, outside the submitted work; A.P.M. reports personal fees from Bayer, Fresenius, and Novartis, outside the submitted work. P.E. reports consultancies from Pfizer, Bristol Myers Squibb, Biomarin, Cytokinetics, and NovoNordisk and grant funding from Sarepta, outside the submitted work. L.Z., S.M., A.A., A.L.P.C., G.L., C.L., P.C., M.T., T.O., G.N., D.K., A.B., M.G., and J.R.G.B. have nothing to disclose.

Data Availability

The data underlying this article cannot be shared publically as consent of dissemination of patient data was not obtained.

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Ethical Approval

Written informed consent was obtained from all participants or their parents/guardians prior to enrolment, and the study received local ethical approval in accordance with each participating centre's governance requirements.

Pre-registered Clinical Trial Number

None supplied.

Appendix

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