Journal of the American Heart Association

ORIGINAL RESEARCH

Clinical Features and Outcomes of Pediatric *MYH7*-Related Dilated Cardiomyopathy

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BACKGROUND: Although genetic variants in *MYH7* are the most frequent cause of pediatric genetic dilated cardiomyopathy (DCM), there are no studies available describing this entity. We sought to describe clinical features, analyze variant location, and explore predictors of bad prognosis in pediatric *MYH7*-related DCM.

METHODS AND RESULTS: We evaluated clinical records from 44 patients (24 men; median age at diagnosis, 0.54 [interquartile range, 0.01–10.8] years) with pathogenic/likely pathogenic variants in *MYH7* diagnosed with DCM at pediatric age (<18 years) followed at 13 international centers. We also explored risk factors associated with a composite end point of end-stage heart failure defined as heart transplantation or heart failure–related death. Twenty-two patients (50%) were diagnosed at age <6 months, including 7 (16%) at birth. Left ventricular (LV) hypertrabeculation features were present in 15 (38%), particularly among patients with genetic variants in the head domain. After a median follow-up of 6.1 years (interquartile range, 1.9–13.4), 15 patients (36%) required a heart transplant (n=14) or died due to end-stage heart failure (n=1), 15 patients (36%) persisted with systolic dysfunction despite treatment, 12 (29%) had a significant increase in LV ejection fraction, and 2 were lost to follow-up. Overall, end-stage heart failure event rate was 25% at 5 years. New York Heart Association class III to IV (hazard ratio [HR], 7.67 [95% CI, 2.16–27.2]; *P*=0.002) and LV ejection fraction ≤35% (HR, 4.00 [95% CI, 1.11–14.4]; *P*=0.03) were the best predictors of bad prognosis.

CONCLUSIONS: Pediatric *MYH7*-related DCM is characterized by early onset, frequent LV hypertrabeculation, and poor prognosis. Advanced New York Heart Association class and low LV ejection fraction emerged as predictors of end-stage heart failure.

Key Words: dilated cardiomyopathy ■ genetics ■ *MYH7* ■ pediatric

Dilated cardiomyopathy (DCM) is a heterogeneous disease defined by left ventricular (LV) systolic dysfunction that can be caused by toxic substances, infectious agents, inflammation, genetic abnormalities, or an intertwinement of these factors.[1–3] During the past decade, genes have been in the spotlight providing valuable information about specific subtypes of DCM, leading the transition to a more personalized approach.[4,5]

Although DCM is predominantly an adult-onset disease, there is a significant proportion of patients that are diagnosed at pediatric age, mostly during infancy.[6]

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This manuscript was sent to Shaan Khurshid, MD, MPH, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036208

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Pediatric *MYH7*-related dilated cardiomyopathy is a condition characterized by early onset, frequent left ventricular hypertrabeculation, and poor prognosis in terms of advanced heart failure.

What Are the Clinical Implications?

- Relatives of patients with MYH7-related dilated cardiomyopathy who are potential carriers would benefit from early clinical and genetic screening.
- Cases identified during childhood might benefit from early referral to tertiary centers with pediatric heart transplantation programs, especially in the presence of advanced functional class (New York Heart Association III–IV).

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
ESHF	end-stage heart failure
HCM	hypertrophic cardiomyopathy
HT	heart transplantation
LVRR	left ventricular reverse remodeling
NYHA	New York Heart Association

Moreover, DCM in children exhibits worse outcomes compared with adults with a high incidence of heart transplantation (HT) and death.[7,8] Recent series have shown that 30% to 37% of pediatric DCM is caused by gene variants in multiple genes but with a clear predominance of genes coding for sarcomeric proteins, including *MYH7*, *TTN*, and *TNNT2*.[9–11]

MYH7 encodes for β-myosin heavy chain, a key component of the cardiac sarcomere, and has been reported to be the most frequently affected gene in pediatric DCM in the 2 largest cohorts of pediatric DCM cases genotyped to date, representing 21% to 25% of cases with pathogenic variants.[10,11] *MYH7*-related DCM features have been recently described in an international DCM collaboration and include frequent presence of hypertrabeculation features, poor response to medical treatment, and the predominance of heart failure (HF)-related events over ventricular arrhythmias that are relatively infrequent and limited to patients with severe systolic dysfunction. In addition, a significant proportion of pediatric-onset cases were described.[12,13] Despite the prominent role of *MYH7*-associated DCM in pediatric DCM, there have not been specific studies describing the natural history and clinical characteristics of *MYH7*-associated DCM in children. Moreover, clinical predictors of bad prognosis in this population are unknown.

The aim of the present study was to describe phenotypic characteristics and prognosis of *MYH7*-related pediatric DCM. In addition, we sought to explore specific gene hotspots associated with this entity and to analyze possible predictors of bad outcomes that could improve clinical management of these patients.

METHODS

Study Population

Inherited cardiac disease units and cardiomyopathy clinics in Europe and the United States were invited to participate in this longitudinal retrospective cohort study. The cohort comprised pediatric patients (aged <18 years at time of DCM diagnosis) with DCM defined as LV ejection fraction (LVEF) ≤50% in patients with the absence of myocarditis, metabolic disorders, or complex congenital heart defects and who carried a pathogenic or likely pathogenic variant in *MYH7*. Patients with a previous diagnosis of hypertrophic cardiomyopathy (HCM) or family history of HCM were excluded to avoid possible inclusion of patients with end-stage HCM. In addition, patients with *MYH7* variants predominantly associated with HCM phenotype or with concomitant pathogenic or likely pathogenic variants in other genes related to cardiomyopathies were excluded.

The study was approved by the Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Helsinki Declaration; written informed consent was waived by the committee. The authors from each participating center guarantee the integrity of data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Genetic Testing and Interpretation

Genetic testing was performed at participating centers or at accredited genetic laboratories. Genetic variant interpretation was centrally curated following American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines adapted for *MYH7*.[14]

Pathogenic and likely pathogenic variants were grouped according to the 3 main domains of β-myosin heavy chain using transcript NM_000257.4: globular head (S1) containing ATP- and actin-binding sites

and a lever domain (amino acids 1–847); neck region (S2) (amino acids 848–1216); and an α helical tail also known as light meromyosin (amino acids 1217–1936).[15] Distribution according to head subdomains were also analyzed including ATP-binding site (amino acids 130–260) and actin-binding site (amino acids 385–515 and 577–611).[16]

Data Acquisition

Data were retrieved and anonymized by each center from medical records. The data set included demographics, family history, signs, symptoms, and treatment at first evaluation. Complementary tests including ECG, Holter ECG, echocardiography, and cardiac magnetic resonance (when performed), both at first and last evaluation, were also included. Echocardiographic measurements were indexed as *Z* scores on the basis of the Boston Children's Hospital calculator (www.zscore.chboston.org). For patients with missing height or weight values (n=9), weight and height were imputed on the basis of standard estimations based on age and sex.[17] LV hypertrabeculation was defined according to Jenni criteria.[18] Patients whose available complementary tests were beyond the age of 18 were excluded from baseline characteristics analysis.

Events during follow-up included device implantation, atrial fibrillation, ventricular arrhythmias, implantable cardioverter-defibrillator therapies for ventricular arrhythmias, HF admission, LV assist device implantation, HT, and death.

Study End Points

End-stage heart failure (ESHF) was defined as HT or HF-related death and used as a combined end point of bad prognosis. Association between baseline characteristics and ESHF was analyzed to identify clinical predictors of bad prognosis. LV reverse remodeling (LVRR) was defined as either LV normalization (LVEF improvement to ≥50% with a ≥5% LVEF increment at the last follow-up) or an absolute increase in LVEF by ≥10% at the last follow-up from baseline, as previously described.[19] Clinical status at last follow-up was categorized in 3 groups: HT/death, LVRR, and persistent dysfunction for those alive not meeting LVRR criteria.

Statistical Analysis

Results are presented as mean±SD for continuous variables and as number and percentage for categorical variables. Student's *t* test and ANOVA tests were used to compare continuous variables with normal distribution assessed by the Shapiro–Wilk test, whereas nonparametric Wilcoxon rank-sum or Kruskal–Wallis tests were applied for those not meeting normal distribution. Categorical variables were compared between groups with the parametric χ^2 test or nonparametric Fisher's exact test. Cumulative incidence with Kaplan–Meier curves were used to describe ESHF events, and follow-up was censored at the time of HT. Patients who were evaluated only once at participating centers and lost to follow-up were excluded from transplant-free survival analysis. Cox proportional hazard regression was performed to assess the association between baseline characteristics and ESHF in univariate analysis. Continuous variables that were statistically significant were dichotomized on the basis of sample distribution (median). Discriminatory capacity was estimated by Harrell's C-statistic among predictors. Multivariable analysis was discarded due to a limited sample size. STATA software version 15.1 (StataCorp, College Station, TX) was used for statistical analysis. A 2-tailed *P* value <0.05 was considered statistically significant.

RESULTS

Information regarding 71 patients was submitted from 13 centers. The flowchart for patient selection is displayed in Figure 1 (Figure S1). A total of 7 patients were excluded for various reasons: 2 had been previously diagnosed with HCM, 2 had an intrauterine fetal death, 1 had family history of HCM, 1 did not have appropriate clinical information, and 1 exhibited a concomitant pathogenic gene variant (2q31.1 deletion and a *LOXDH1* likely pathogenic variant). In addition, 2 patients were excluded because they carried *MYH7* variants that were predominantly associated with HCM. Finally, variant classification of the remaining 62 patients identified 18 patients with variants classified as variants of unknown significance. Therefore, the final cohort included 44 patients encompassing 33 independent families. Twenty-five patients (57%) were probands, and the rest (n=19 [43%]) were relatives diagnosed through cascade screening. Regarding country of origin, 26 patients (59%) were followed up in European centers, whereas 18 (41%) were from US centers.

Age of DCM Onset

Figure 2 portrays distribution of patients according to age of DCM onset and shows that 22 patients (50%) were diagnosed during the first 6 months of life, whereas 50% of patients were diagnosed during pediatric age with a balanced distribution across age groups. Of particular clinical interest is the fact that 7 patients (16%) were diagnosed immediately at birth or, in 1 case, in utero during fetal echocardiographic

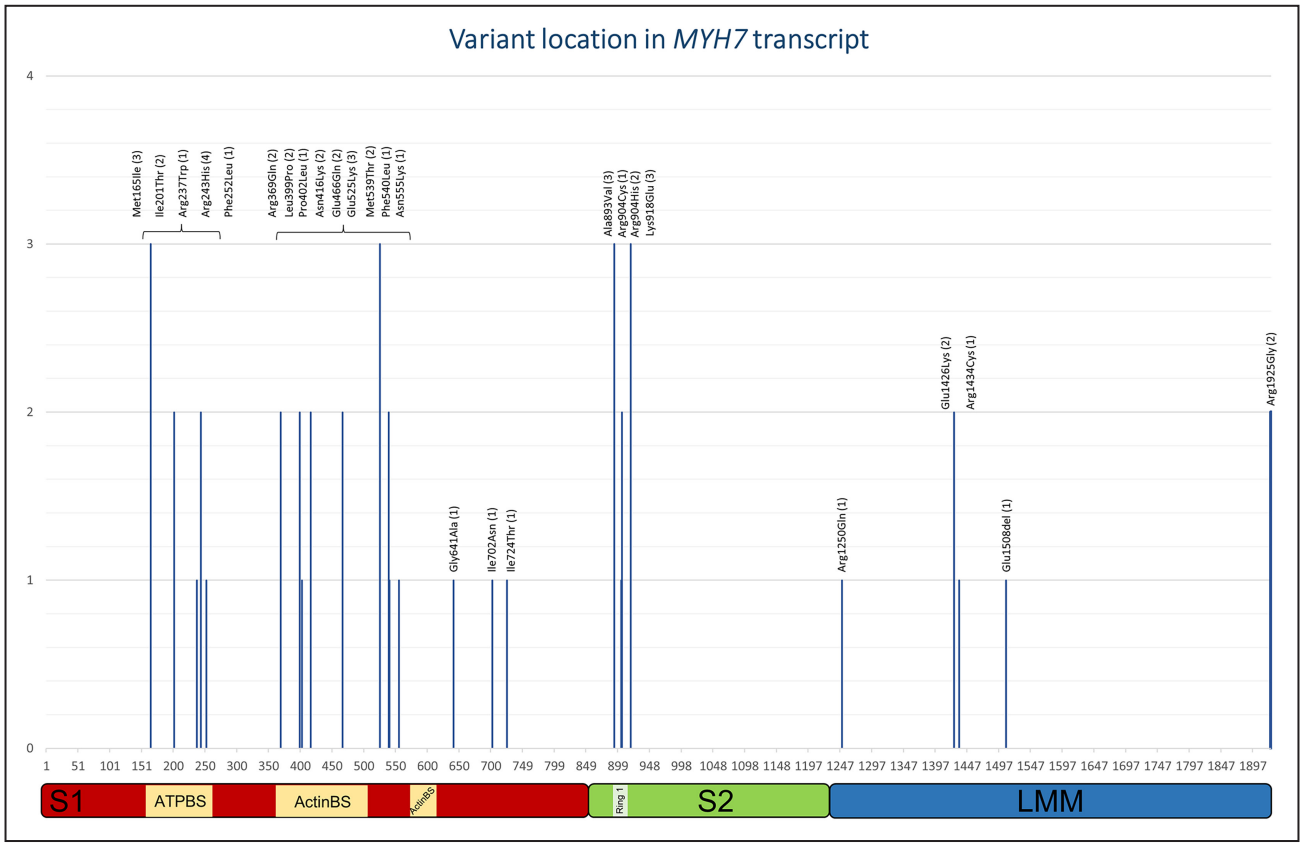

Figure 1. Variant location in *MYH7* transcript.
The figure displays the location of variants included in this cohort, its domains within myosin (S1, S2, LMM) and its subdomains (ATPBS, ActinBS and Ring 1). S1: globular head (amino acids 1–847); S2: neck region (amino acids 848–1216); light meromyosin (amino acids 1217–1936); ATP-binding site (amino acids 130–260); actin-binding site (amino acids 385–515 and 577–611); Ring 1 (amino acids 894–907).

assessment. The year of diagnosis ranged from 1993 to 2021 in our cohort, with 1 outlier that was diagnosed in 1976.

Clinical Characteristics

Baseline characteristics at pediatric age were available for 41 patients, as 3 patients were initially diagnosed with DCM at age <18 years but were first assessed at participating centers after age 18 years. Overall, 27 individuals (66%) exhibited a family history of DCM. Although mean age at first evaluation was 5.3 years, the median age was 0.6 (interquartile range, 0.1–12.5). Of note, 13 patients (32%) were in New York Heart Association (NYHA) class IV at first evaluation. Overall, atrial fibrillation, intraventricular conduction disturbances, and frequent ventricular paroxysmal beats were uncommon (Table 1). In contrast, mean LVEF was 33.9±12.1%, with 19 patients (48%) showing LVEF ≤35% and 15 patients (38%) displaying concomitant hypertrabeculation features, respectively. Late gadolinium enhancement was found in 2 cases (17%) among the 12 patients assessed with cardiac magnetic resonance. Late gadolinium enhancement patterns were described as subendocardial in the septum and papillary muscles and as subepicardial in the inferior segment combined with subendocardial in the anterior segments. Concomitant skeletal muscle disease defined as Laing distal muscular dystrophy was present only in 1 patient (p.Glu1508del).

Mode of Onset and Clinical Course

Figure 3 summarizes mode of onset and clinical course. Twelve patients (27%) had a cardiogenic shock as a first manifestation of the disease, while 18 (41%) were diagnosed incidentally in absence of symptoms (n=3) or family screening (n=15). Among patients admitted due to cardiogenic shock, 3 received an HT during admission, and 1 died due to refractory HF. Overall median follow-up was 6.1 years (interquartile range, 1.9–13.4). Follow-up information was not available for 2 individuals.

Regarding medical treatment, 34 subjects (94%) received angiotensin-converting enzyme inhibitors,

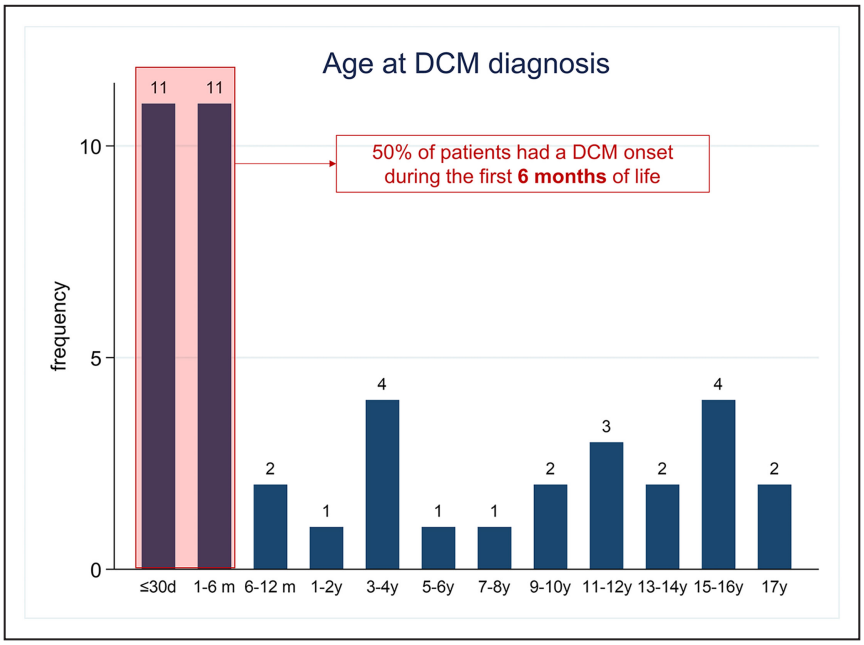

Figure 2. Age at DCM diagnosis.
Half of patients (50% were diagnosed during the first 6 mo of life including 7 patients (15.9%) that were diagnosed immediately at birth. DCM indicates dilated cardiomyopathy.

13 (36%) β blockers, 14 (39%) mineralocorticoid receptor antagonist, and 8 (22%) digoxin. During follow-up, 11 additional patients required an HT, and median age at HT was 8.0 years (interquartile range, 0.9–16.6). On the other side of the spectrum, 12 patients (29%) had a significant LVRR at last follow-up. Finally, 15 patients (36%) remained with persistent systolic dysfunction, although they were in NYHA class I (n=13) or NYHA class II (n=2), and none required further HF admissions. Regarding other relevant clinical events, 3 patients (8%) presented de novo atrial fibrillation during follow-up, only 1 patient had a sustained ventricular tachycardia in the context of cardiogenic shock, and 2 received an implantable cardioverter-defibrillator in primary prevention but have not required therapies or shocks during follow-up. No episodes of sudden cardiac death have been registered.

ESHF Predictors

Overall, 15 patients had an ESHF event during follow-up, 14 underwent HT, and 1 died due to refractory HF. The event rate from diagnosis was 25.3% at 5 years (Figure 4). Table 2 displays univariate analysis results of predictors of a bad prognosis. Presentation as cardiogenic shock (hazard ratio [HR], 13.3 [95% CI, 1.65–106.5]; *P*=0.02), NYHA class III to IV (HR, 7.67 [95% CI, 2.16–27.2]; *P*=0.002), treatment with a mineralocorticoid receptor antagonist (HR, 3.81 [95% CI, 1.17–12.4]; *P*=0.03), and LVEF ≤35% (HR, 4.00 [95% CI, 1.11–14.4]; *P*=0.03) were all significantly associated with a worse prognosis. Although all predictors showed a remarkable discriminatory capacity, NYHA showed the highest Harrell's C-statistic (0.787 [95% CI, 0.701–0.873]) among categorical variables. Figure 5 displays the Kaplan–Meier curve for ESHF according to the NYHA at first evaluation. Patients in NYHA class III to IV had a 41.2% (95% CI, 22.2–67.5) event rate at 2 years and 58.8% (95% CI, 37.4–81.4) event rate at 5 years. Mineralocorticoid receptor antagonist treatment was significantly associated with severe systolic dysfunction (LVEF ≤35%, 57.9% versus LVEF >35%, 23.8%; *P*=0.05), which suggests it might act as a confounding factor. Other relevant variables including age at DCM diagnosis, sex, year of diagnosis, or variant location were not significantly associated with ESHF. Multivariable analysis was not performed due to the limited sample size and number of events.

Variant Location

The variant location across *MYH7* from the patients included in the study is shown in Figure 1. Criteria applied for classification of variants and variants included in the study are provided in Data S1 and Tables S1 and S2. Most patients (n=28 [63.6%]) carried variants in the head domain (S1), followed by S2 (n=9 [20.5%]) and light meromyosin (n=7 [15.9%]). A closer look at subdomain location showed 3 clear clusters in the head domain variants encompassing the ATP-binding site,

Table 1. Baseline Characteristics of Patients According to *MYH7* Variant Location

	Overall (N=41)	S1 (n=25)	S2 (n=9)	LMM (n=7)	*P* value
Age at DCM diagnosis, y	4.7 (6.3)	5.9 (6.8)	2.0 (3.5)	4.0 (6.7)	0.11
Family history, n (%)	27 (65.9)	16 (64.0)	7 (77.8)	4 (57.1)	0.73
Female sex, n (%)	20 (48.8)	14 (56.0)	4 (44.4)	2 (28.6)	0.47
Age first evaluation, y	5.3 (6.6)	6.7 (7.1)	2.2 (3.3)	4.2 (7.0)	0.55
Weight, kg	21.7 (22.6)	25.6 (24.3)	11.8 (10.9)	20.3 (26.2)	0.64
Height, cm	97.7 (49.1)	107.0 (51.8)	78.2 (29.7)	89.5 (55.9)	0.35
Ancestry, n (%)					0.21
European	34 (82.9)	22 (88.0)	5 (55.6)	7 (100)	
Asian	1 (2.4)	0 (0)	1 (11.1)	0 (0)	
African	1 (2.4)	1 (4.0)	0 (0)	0 (0)	
Other/mixed	3 (7.3)	1 (4.0)	2 (22.2)	0 (0)	
Not reported	2 (4.9)	1 (4.0)	1 (11.1)	0 (0)	
Clinical status, n (%)					
NYHA class					0.27
I	19 (46.3)	12 (48.0)	4 (44.4)	3 (42.9)	
II	5 (12.2)	5 (20.0)	0 (0.0)	0 (0.0)	
III	4 (9.8)	2 (8.0)	0 (0.0)	2 (28.6)	
IV	13 (31.7)	6 (24.0)	5 (55.6)	2 (28.6)	
Skeletal muscle disease, n (%)	1 (2.4)	0 (0)	0 (0)	1 (14.3)	0.17
Devices, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	…
ECG (N=40), n (%)					
Atrial fibrillation	2 (5)	2 (8.0)	0 (0)	0 (0)	1
QRS morphology, n (%)					0.79
Narrow	34 (85.0)	21 (84.0)	7 (77.8)	6 (100)	
RBBB	1 (2.5)	1 (4.0)	0 (0)	0 (0)	
LBBB	1 (2.5)	1 (4.0)	0 (0)	0 (0)	
NIVCD	4 (10.0)	2 (8.0)	2 (22.2)	0 (0)	
Holter ECG (n=21), n (%)					
PVB/24 h					0.81
0	13 (61.9)	7 (53.9)	4 (80.0)	2 (66.7)	
1–250	8 (38.1)	6 (46.2)	1 (20.0)	1 (33.3)	
>250	0 (0)	0 (0)	0 (0)	0 (0)	
NSVT	2 (9.5)	2 (15.4)	0 (0)	0 (0)	1
Echocardiography (N=40), n (%)					
LVEF, %	33.9 (12.1)	35.9 (10.6)	29.3 (14.9)	32.3 (13.5)	0.49
LVEDD, mm	40.8 (16.0)	42.3 (17.8)	36.0 (12.3)	41.7 (14.2)	0.73
Z score	3.7 (3.8)	3.1 (4.1)	4.5 (3.8)	5.0 (3.1)	0.47
Hypertrabeculation	15 (37.5)	13 (52.0)	2 (22.2)	0 (0)	0.04
Cardiac magnetic resonance (N=12), n (%)					
Late gadolinium enhancement	2 (16.7)	2 (20.0)	0 (0)	…	1

DCM indicates dilated cardiomyopathy; HF, heart failure; LBBB, left bundle-branch block; LMM, light meromyosin; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NIVCD, nonspecific intraventricular conduction delay; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVB, premature ventricular beats; and RBBB, right bundle-branch block.

the actin-binding site, and a third subdomain from position 525 to 555. All variants located in the S2 domain were concentrated in a small region from position 893 to position 918. In contrast, variants located in the light meromyosin region were not clustered in any specific region.

When baseline characteristics were compared among patients grouped by variant location, hypertrabeculation was the only feature that differed across groups (P=0.04), showing a clear predominance in patients with variants in S1 in contrast with light meromyosin (52% versus 0%, P=0.03). Despite the limited sample

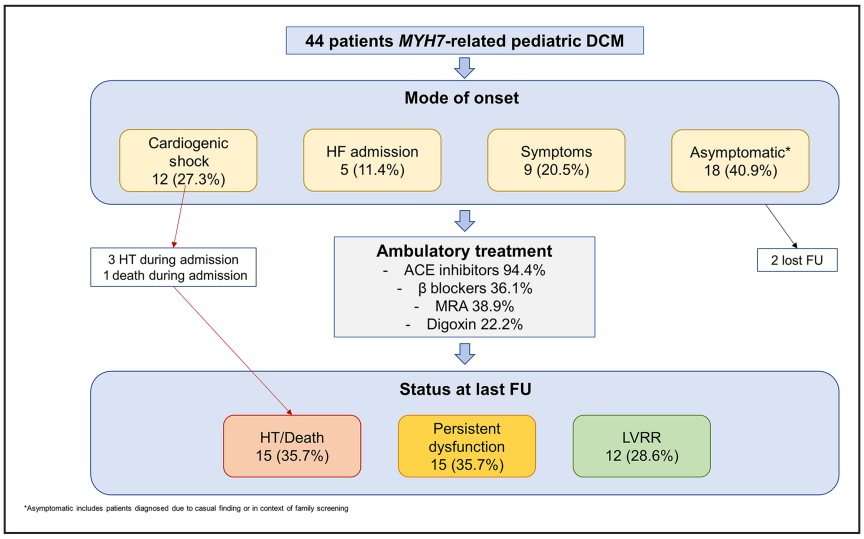

Figure 3. Mode of onset and clinical course.
At last follow-up, 15 patients (36%) required a heart transplantation (n=14) or died (n=1), 15 patients (36%) persisted with systolic dysfunction despite treatment, and 12 (29%) had a significant increase in left ventricular ejection fraction. ACE indicates angiotensin-converting enzyme; DCM, dilated cardiomyopathy; FU, follow-up; HF, heart failure; HT, heart transplantation; LVRR, left ventricular reverse remodeling; and MRA, mineralocorticoid receptor antagonist. *Asymptomatic includes patients diagnosed due to casual finding or in context of family screening.

size, some other tendencies were observed. For example, patients with variants in S2 had a tendency to have a lower age of onset (P=0.11) and more severe symptoms, as most patients (n=5 [55.6%]) were in NYHA class IV at first evaluation (P=0.27), although not reaching statistical significance. No differences were found between groups with respect to ECG findings, LVEF, LV dimensions, or late gadolinium enhancement presence.

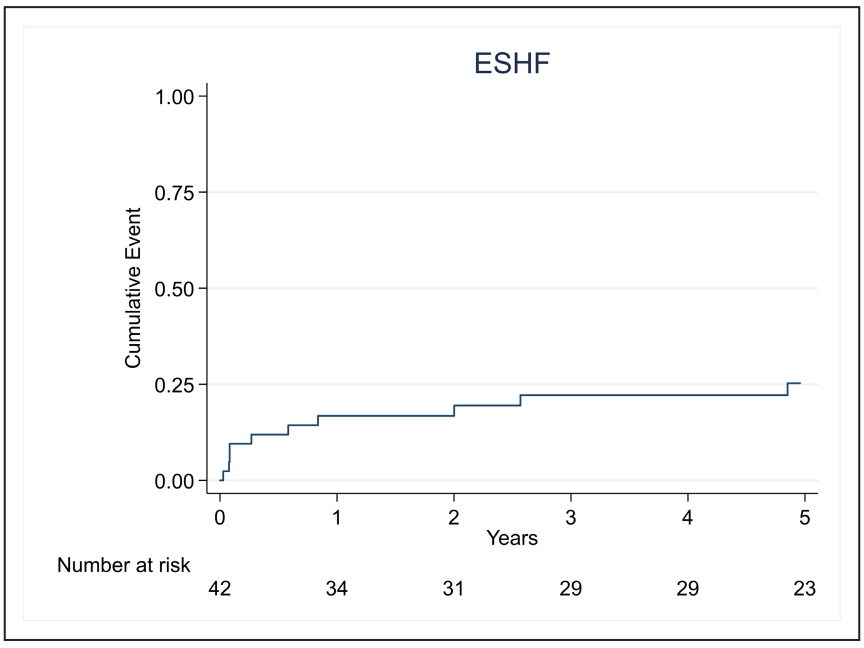

Figure 4. Kaplan–Meier curve of incidence of ESHF.
Overall, 15 patients had an ESHF event during follow up, 14 in the form of HT and 1 as death due to HF. Event rate from diagnosis was established in 25.3% at 5 y. ESHF indicates end-stage heart failure.

Table 2. Predictors of ESHF

	HR 95% CI*	*P* value*	Harrell's C-statistic (95% CI)
Age at DCM diagnosis, y	0.97 (0.89–1.06)	0.53	
Proband	1.64 (0.52–5.20)	0.40	
Female sex	1.59 (0.56–4.48)	0.38	
Year of diagnosis			
Before 2012	Ref	…	
2012 onward	1.6 (0.50–5.17)	0.42	
Clinical status			
Mode of presentation			0.781 (0.678–0.884)
Asymptomatic	Ref	…	
Symptoms	4.90 (0.50–47.7)	0.17	
HF admission	8.0 (0.81–77.2)	0.07	
Cardiogenic shock	13.3 (1.65–106.5)	**0.02**	
NYHA class			**0.787 (0.701–0.873)**
I–II	Ref	…	
III–IV	7.67 (2.16–27.2)	**0.002**	
Medical treatment			
β blockers	0.87 (0.28–2.73)	0.81	
MRA	3.81 (1.17–12.4)	**0.03**	**0.660 (0.523–0.796)**
Digoxin	2.05 (0.67–6.28)	0.21	
ECG			
QRS morphology			
Narrow	Ref	…	
IVCD	0.77 (0.17–3.47)	0.73	
Echocardiography			
LVEF, %	0.92 (0.87–0.97)	0.002	**0.806 (0.687–0.925)**
LVEF dichotomized			
LVEF >35%	Ref	…	
LVEF ≤35%	4.00 (1.11–14.4)	**0.03**	**0.702 (0.583–0.821)**
Hypertrabeculation	1.78 (0.62–5.11)	0.29	
Variant location			
S1	Ref	…	
S2	1.68 (0.50–5.67)	0.40	
Light meromyosin	1.21 (0.32–4.66)	0.78	

Bold values indicates statistically significant *P* values. DCM indicates dilated cardiomyopathy; HF, heart failure; IVCD, intraventricular conduction delay; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and NYHA, New York Heart Association.

*Unadjusted univariate analysis.

DISCUSSION

The present study represents the first cohort to specifically address pediatric *MYH7*-related DCM, the most frequent cause of genetic DCM in childhood. Our results show an aggregation of variants around relevant protein subdomains and a very early age of onset in most cases. Phenotypically, LV hypertrabeculation is frequently observed, especially in variants located in the head domain, while skeletal muscle disease was rare. Overall patients had a grim prognosis, with one third of patients requiring an HT, whereas only a quarter showed LVRR with standard treatment. Furthermore, we identified advanced NYHA class and low LVEF as good predictors of outcomes that could help clinicians in assessing prognosis and to plan therapeutic alternatives in this complicated group of patients where HT/LV assist device are frequently not readily available.

Our study shows that variant location in children follows a similar distribution as in general *MYH7*-related DCM cohorts, as most variants were located in the S1 domain. Interestingly, variants were mainly located across certain functional subdomains including ATP-binding site and actin-binding site, with a third cluster between 525 and 555 residues positions. Among this last group, the p.Glu525Lys variant is of special interest because it was found in 3 independent families and in all cases exhibited an early age of onset (median, 1.6 [interquartile range, 1.0–4.3] months) and a bad prognosis (all required HT), similar to previous cases described.[20] Functional studies have demonstrated that this amino acid is located in a sensitive region of the head called the mesa trail that is implicated in the interaction with S2 during a relaxed state thanks to electrostatic attraction; this conformation is known as interacting heads motif. The substitution of a negative amino acid (Glu) for a positive amino acid (Lys) would lead to higher attraction in a relaxed state, translating into fewer heads available for contraction.[21] Surprisingly for us, a fourth cluster was found in the S2 domain that overall represented the most infrequent location for pathogenic variant location in the overall cohort.[12] These variants (p.Ala893Val, p.Arg904Cys, p.Arg904His, p.Lys918Glu) were located over a relevant subdomain in S2 named Ring 1 (amino acids 894–907) that binds to the head domain during interacting heads motif. Remarkably, 3 of the 4 variants would provoke a change in amino acid charge that would disrupt normal electrostatic interaction.[21] Although this subdomain is already encompassed by a defined hotspot (amino acids 181–937) for *MYH7* variant interpretation, special attention is warranted for clinical interpretation of variants in this region in the future, especially if related to pediatric DCM.[14] Of note, myosin activators (omecamtiv and danicamtiv) that increase the number of myosin–actin interactions by disrupting interacting heads motif might be particularly interesting for patients affected by variants in this region, as they would rescue systolic function of these cardiomyocytes.[22,23]

From a phenotypic point of view, our results show that pediatric *MYH7*-related DCM is characterized by

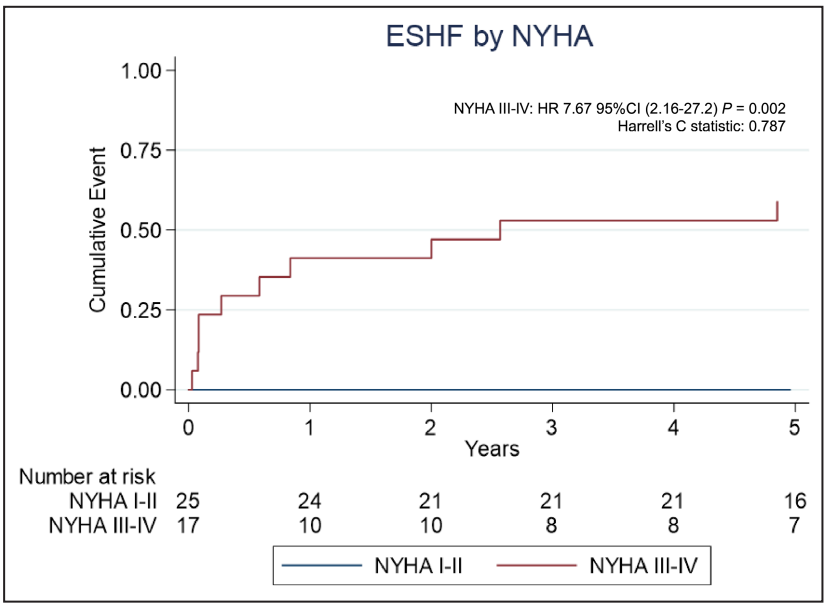

Figure 5. Kaplan–Meier curve of incidence of end-stage heart failure according to NYHA at baseline.
NYHA showed the highest discrimination capacity (Harrell's C-statistic=0.787). Patients in NYHA class III–IV had a 41.2% event rate at 2 y and 58.8% event rate at 5 y. ESHF indicates end-stage heart failure; HR, hazard ratio; and NYHA, New York Heart Association.

a very early age of onset, in most cases during the first year of life and at birth in a significant proportion of patients. This finding is consistent with previously published pediatric *MYH7*-related DCM cases and differs from other forms of pediatric genetic DCM such as *TTN* or *DMD* that is more frequently found in older children.[6,11]

In line with what has been described in adult *MYH7*-related DCM cohorts, LV hypertrabeculation features were found in a remarkable proportion of patients, and ventricular arrhythmias were rare.[12]

In addition, the clinical presentation and course of pediatric *MYH7*-related DCM seems to be defined by the severity of HF complications. Currently, there is controversy about the role of genetics on outcomes compared with other causes of DCM in pediatric DCM, as overall prognosis is poor with higher rates of death and HT than in adult patients.[7] Two large US cohorts did not find differences in terms of HT or death between patients with causative variants and those gene elusive,[9,10] while 2 European cohorts showed higher mortality rates in pediatric DCM patients with a positive genetic test.[6,11] Having a closer look into studies that have described clinical course of pediatric DCM according to specific genes, a recent study from the Netherlands suggested a relatively higher transplant-free survival of patients with *MYH7*-related DCM compared with a combined group of other patients who are gene positive.[11] A possible explanation to the discordance of this work and our findings is the limited number of patients examined in this study (8 individuals with only 1 receiving an HT). Our results, based on a larger population, are not so optimistic and showed a 25% risk of ESHF at 5 years despite inclusion of relatives and not only probands. Prognosis was especially adverse for patients with advanced functional class (NYHA class III–IV) or severe systolic dysfunction (LVEF ≤35%) at baseline. Both variables were also found as good predictors of ESHF in a previous study of pediatric DCM, but as opposed to that cohort, our work did not find an association between β blocker prescription and clinical outcomes in our cohort.[7]

Clinical Implications

Our work has important clinical implications despite its limited sample size. First of all, our findings support an early clinical and genetic screening of relatives that should include fetal surveillance through echocardiography in cases when variant transmission has not been averted by embryo selection. If systolic dysfunction is suspected or confirmed, delivery might be better planned in centers with available specialized cardiac support for children. In line with the previous comment, patients diagnosed with *MYH7*-related DCM should have an early referral to tertiary centers with LV assist device and HT programs considering the high incidence of ESHF at early ages. In particular,

children with p.Glu525Lys variant might benefit from closer follow-up considering the poor outcomes observed in subjects with this specific variant both in our study and in the literature. Our findings also suggest that LVRR is not frequent despite medical treatment. Finally, our careful analysis of the variants implicated suggest that myosin activators could be a promising alternative for *MYH7*-related pediatric DCM, although a major hurdle remains in the path because pediatric patients have been excluded systematically in clinical trials.[24,25] We hope that mounting evidence about the relevance of *MYH7* in pediatric DCM combined with evidence about its bad prognosis and LVRR might encourage investigators to include this subpopulation in future clinical trials.

LIMITATIONS

Some limitations should be taken into account. First, our study was a retrospective longitudinal cohort study involving a wide time frame and also different countries, leading to significant heterogeneity regarding medical care. Although sample size is remarkable for a cohort focused on pediatric DCM in a single gene, the final number of patients was limited, particularly for predictive analysis. Additionally, exclusion of phenotype-negative carriers of *MYH7* variants and selection of pediatric cases of DCM limits generalizability of our findings to all *MYH7* variant carriers and should not guide clinical management of carriers of *MYH7* variants in other clinical contexts, such as incidental findings of exome or genome sequencing.

CONCLUSIONS

Pediatric *MYH7*-related DCM is caused by variants mostly located in certain relevant protein subdomains. Its main features include early age of onset, frequent presence of LV hypertrabeculation features, and poor prognosis in terms of absence of LVRR and frequent course toward ESHF. Advanced NYHA class and low LVEF emerged as good predictors of ESHF that might help to tailor therapeutic alternatives.

ARTICLE INFORMATION

Received July 16, 2024; accepted September 11, 2024.

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Sources of Funding

This study was funded by Instituto de Salud Carlos III through the projects PI18/0004, PI20/0320, and PT17/0015/0043 (cofunded by the European Regional Development Fund/European Social Fund ["A way to make Europe"/"Investing in your future"]). The Centro Nacional de Investigaciones Cardiovasculares is supported by the Instituto de Salud Carlos III, Ministry of Science and Innovation (MCIN), the Pro-CNIC Foundation, and the Severo Ochoa Centers of Excellence program (CEX2020-001041-S). The Hospital Universitario Puerta de Hierro, the Hospital Sant Joan de Déu, Institute for Clinical and Experimental Medicine, the University Medical Centre Utrecht, the Hospital General Universitario Gregorio Marañón, and the Hospital Universitario Virgen de la Arrixaca are members of the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart: ERN GUARD–Heart (http://guardheart.ern-net.eu). Dr de Frutos receives grant support from Instituto de Salud Carlos III (CM20/00101). Dr Kubanek received grant support from the Ministry of Health of the Czech Republic (NV19-08-00122), MH CZ—DRO (Institute for Clinical and Experimental Medicine—IKEM, IN 00023001), and by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Program EXCELES, Project No. LX22NPO5104)—Funded by the European Union—Next Generation EU. This work was supported by the Netherlands Cardiovascular Research Initiative with the support of the Dutch Heart Foundation (CVON2014-40 DOSIS, DCVA [Dutch Cardiovascular Alliance] 2020B005 DoubleDose to Drs Jansen and Annette F Baas) and the Dutch Heart Foundation (Dekker 2015T041 to Drs Annette F Baas and Jansen).

Disclosures

None.

Supplemental Material

Data S1

REFERENCES

1. Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. *Eur J Heart Fail*. 2018;20:228–239. doi: 10.1002/ejhf.1103

2. Sinagra G, Elliott PM, Merlo M. Dilated cardiomyopathy: so many cardiomyopathies! *Eur Heart J*. 2020;41:3784–3786. doi: 10.1093/eurheartj/ehz908
3. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, Toepfer CN, Getz K, Gorham J, Patel P, et al. Genetic variants associated with cancer therapy-induced cardiomyopathy. *Circulation*. 2019;140:31–41. doi: 10.1161/CIRCULATIONAHA.118.037934
4. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, Daubert JP, de Chillou C, DePasquale EC, Desai MY, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019;16:e301–e372. doi: 10.1016/j.hrthm.2019.05.007
5. Escobar-Lopez L, Ochoa JP, Mirelis JG, Espinosa MÁ, Navarro M, Gallego-Delgado M, Barriales-Villa R, Robles-Mezcua A, Basurte-Elorz MT, Gutiérrez García-Moreno L, et al. Association of genetic variants with outcomes in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol*. 2021;78:1682–1699. doi: 10.1016/j.jacc.2021.08.039
6. Jammal Addin MB, Young D, McCarrison S, Hunter L. Dilated cardiomyopathy in a national paediatric population. *Eur J Pediatr*. 2019;178:1229–1235. doi: 10.1007/s00431-019-03404-w
7. Puggia I, Merlo M, Barbati G, Rowland TJ, Stolfo D, Gigli M, Ramani F, Di Lenarda A, Mestroni L, Sinagra G. Natural history of dilated cardiomyopathy in children. *J Am Heart Assoc*. 2016;5:1–10. doi: 10.1161/JAHA.116.003450
8. Singh RK, Canter CE, Shi L, Colan SD, Dodd DA, Everitt MD, Hsu DT, Jefferies JL, Kantor PF, Pahl E, et al. Survival without cardiac transplantation among children with dilated cardiomyopathy. *J Am Coll Cardiol*. 2017;70:2663–2673. doi: 10.1016/j.jacc.2017.09.1089
9. Quiat D, Witkowski L, Zouk H, Daly KP, Roberts AE. Retrospective analysis of clinical genetic testing in pediatric primary dilated cardiomyopathy: testing outcomes and the effects of variant reclassification. *J Am Heart Assoc*. 2020;9:e016195. doi: 10.1161/JAHA.120.016195
10. Khan RS, Pahl E, Dellefave-Castillo L, Rychlik K, Ing A, Yap KL, Brew C, Johnston JR, McNally EM, Webster G. Genotype and cardiac outcomes in pediatric dilated cardiomyopathy. *J Am Heart Assoc*. 2022;11:11. doi: 10.1161/JAHA.121.022854
11. van der Meulen MH, Herkert JC, den Boer SL, du Marchie Sarvaas GJ, Blom N, ten Harkel ADJ, Breur HMPJ, Rammeloo LAJ, Tanke R, Marcelis C, et al. Genetic evaluation of a nation-wide Dutch pediatric DCM cohort: the use of genetic testing in risk stratification. *Circ Genom Precis Med*. 2022;15:e002981. doi: 10.1161/CIRCGEN.120.002981
12. de Frutos F, Ochoa JP, Navarro-Peñalver M, Baas A, Bjerre JV, Zorio E, Méndez I, Lorca R, Verdonschot JA, García-Granja PE, et al. Natural history of MYH7-related dilated cardiomyopathy. *J Am Coll Cardiol*. 2022;80:1447–1461. doi: 10.1016/j.jacc.2022.07.023
13. Jansen M, de Brouwer R, Hassanzada F, Schoemaker AE, Schmidt AF, Kooijman-Reumerman MD, Bracun V, Slieker MG, Dooijes D, Vermeer AMC, et al. Penetrance and prognosis of MYH7 variant-associated cardiomyopathies. *JACC: Heart Fail*. 2024;12:134–147. doi: 10.1016/j.jchf.2023.07.007
14. Kelly MA, Caleshu C, Morales A, Buchan J, Wolf Z, Harrison SM, Cook S, Dillon MW, Garcia J, Haverfield E, et al. Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel. *Genet Med*. 2018;20:351–359. doi: 10.1038/gim.2017.218
15. Colegrave M, Peckham M. Structural implications of β-cardiac myosin heavy chain mutations in human disease. *Anat Rec*. 2014;297:1670–1680. doi: 10.1002/ar.22973
16. Moore JR, Leinwand L, Warshaw DM. Understanding cardiomyopathy phenotypes based on the functional impact of mutations in the myosin motor. *Circ Res*. 2012;111:375–385. doi: 10.1161/CIRCRESAHA.110.223842
17. Onis M. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr*. 2007;95:76–85.
18. Jenni R. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart*. 2001;86:666–671. doi: 10.1136/heart.86.6.666
19. Verdonschot JAJ, Hazebroek MR, Derks KWJ, Barandiarán Aizpurua A, Merken JJ, Wang P, Bierau J, van den Wijngaard A, Schalla SM, Abdul Hamid MA, et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. *Eur Heart J*. 2018;39:864–873. doi: 10.1093/eurheartj/ehx808
20. Anon. ClinVar: MYH7 p.Glu525Lys. https://www.ncbi.nlm.nih.gov/clinvar/variation/132925/
21. Woodhead JL, Craig R. The mesa trail and the interacting heads motif of myosin II. *Arch Biochem Biophys*. 2020;680:108228. doi: 10.1016/j.abb.2019.108228
22. Kampourakis T, Zhang X, Sun Y-B, Irving M. Omecamtiv mercabil and blebbistatin modulate cardiac contractility by perturbing the regulatory state of the myosin filament. *J Physiol*. 2018;596:31–46. doi: 10.1113/JP275050
23. Bernier TD, Buckley LF. Cardiac myosin activation for the treatment of systolic heart failure. *J Cardiovasc Pharmacol*. 2021;77:4–10. doi: 10.1097/FJC.0000000000000929
24. Voors AA, Tamby JF, Cleland JG, Koren M, Forgosh LB, Gupta D, Lund LH, Camacho A, Karra R, Swart HP, et al. Effects of danicamtiv, a novel cardiac myosin activator, in heart failure with reduced ejection fraction: experimental data and clinical results from a phase 2a trial. *Eur J Heart Fail*. 2020;22:1649–1658. doi: 10.1002/ejhf.1933
25. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384:105–116. doi: 10.1056/NEJMoa2025797