Penetrance and prognosis of *MYH7* variant-associated cardiomyopathies: Results from a Dutch multicenter cohort study

Mark Jansen, MD [1-4] *

Remco de Brouwer, MD [3,5] *

Fahima Hassanzada, MD [1,4]

Angela E Schoemaker, MSc [1,4]

Amand F Schmidt, PhD [2,4,6,7]

Maria D Kooijman-Reumerman, MSc [1,4]

Valentina Bracun, MD [5]

Martijn G Slieker, MD PhD [4,8]

Dennis Dooijes, PhD [1,4]

Alexa MC Vermeer, MD PhD [4,9]

Arthur AM Wilde, MD PhD [4,7]

Ahmad S Amin, MD PhD [4,7]

Ronald H Lekanne Deprez, PhD [4,9]

Johanna C Herkert, MD PhD [10]

Imke Christiaans, MD PhD [10]

Rudolf A de Boer, MD PhD [5,11]

Jan DH Jongbloed, PhD [10]

J Peter van Tintelen, MD PhD [1,3,4]

Folkert W Asselbergs, MD PhD [2,4,6,7,12]

Annette F Baas, MD PhD [1,4]

* These authors contributed equally

Affiliations:

1 Department of Genetics, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

2 Department of Cardiology, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

3 Netherlands Heart Institute, Utrecht, the Netherlands

4 'Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart' (ERN GUARDHEART; http://guardheart.ern-net.eu)

5 University of Groningen, University Medical Centre Groningen, Department of Cardiology, Groningen, the Netherlands

6 Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom

7 Amsterdam UMC location University of Amsterdam, Department of Cardiology, Amsterdam, the Netherlands; Amsterdam Cardiovascular Sciences, Heart Failure and arrhythmias, Amsterdam, the Netherlands

8 Department of Pediatric Cardiology, University Medical Centre Utrecht, Utrecht University, the Netherlands

9 Department of Human Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

10 University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, the Netherlands

11 Department of Cardiology, Thorax Center, Erasmus University Medical Center, Erasmus University Rotterdam, Rotterdam, The Netherlands.

12 Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom

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Address for correspondence:

Mark Jansen

Department of Cardiology, University Medical Centre Utrecht

Internal mail no HTx Secr. (E03.511), Postbus 85500, 3508 GA Utrecht, The Netherlands

Tel: +316-382 415 36, Fax: +3188-755 50 03

E-mail: m.jansen-48@umcutrecht.nl

Abstract

Background: *MYH7* variants cause hypertrophic (HCM), non-compaction (NCCM) and dilated cardiomyopathy (DCM). Screening of relatives of genetic cardiomyopathy patients is recommended from 10-12 years onwards, irrespective of the affected gene and phenotype.

Objective(s): To study penetrance and prognosis of *MYH7* variant-associated cardiomyopathies.

Methods: In this multicenter cohort study, penetrance and major cardiomyopathy-related events (MCE) were assessed in carriers of (likely) pathogenic *MYH7* variants using Kaplan-Meier curves and log-rank tests. Prognostic factors were evaluated using Cox regression with time-dependent coefficients.

Results: In total, 581 subjects (30.1% index patients, 48.4% male, median age 37.0 years [interquartile range 19.5-50.2]) were included. HCM was diagnosed in 226 subjects, NCCM in 70 and DCM in 55. Early penetrance and MCE (age <12 years) were common among NCCM- (21.2% and 12.0%, respectively) and DCM-associated variant carriers (15.3% and 10.0%), compared to HCM-associated variant carriers (2.9% and 2.1%). Penetrance was significantly increased in carriers of converter region variants (adjusted hazard ratio [95% confidence interval]: 1.87 [1.15-3.04], p=0.012), and at ages ≤1 year in NCCM-/DCM-associated variant carriers (21.17 [4.81-93.20], p<0.001) and subjects with a family history of early MCE (2.45 [1.09-5.50], p=0.030). Risk of MCE was increased in subjects with a family history of early MCE (1.82 [1.15-2.87], p=0.010) and at ages ≤5 years in NCCM-/DCM-associated variant carriers (38.82 [5.16-291.88], p<0.001).

Conclusions: *MYH7* variants can cause cardiomyopathies and MCE at a young age. Screening at younger ages may be warranted, particularly in carriers of NCCM- or DCM-associated variants and/or with a family history of MCE at <12 years.

Keywords: Cardiomyopathy, *MYH7*, myosin, prognosis, penetrance, screening

Abbreviations

DCM = dilated cardiomyopathy

$DCM_{variant}$ = dilated cardiomyopathy-associated *MYH7* variant

HCM = hypertrophic cardiomyopathy

$HCM_{variant}$ = hypertrophic cardiomyopathy-associated *MYH7* variant

LVEF = left ventricular ejection fraction

MCE = major cardiomyopathy-related events

MYH7 = myosin heavy chain 7

MHC-β = myosin heavy chain-beta

NCCM = non-compaction cardiomyopathy

$NCCM_{variant}$ = non-compaction cardiomyopathy-associated *MYH7* variant

Introduction

The myosin heavy chain 7 (*MYH7*) gene encodes myosin heavy chain beta (MHC-β), a predominant protein in the thick myosin filaments of ventricular cardiomyocyte sarcomeres (1,2). *MYH7* variants are identified in 12-16% of patients with hypertrophic cardiomyopathy (HCM), 6-14% with non-compaction cardiomyopathy (NCCM), and 2-5% with dilated cardiomyopathy (DCM) (3-5).

Clinical severity is highly variable with incomplete penetrance (6-8). Still, differences in prognosis have been reported for *MYH7* variants compared to other genotypes: *MYH7* variants were associated with an earlier onset and higher risk of heart failure events in HCM patients and a lower risk of a composite endpoint of heart failure hospitalization, end-stage heart failure, malignant ventricular arrhythmia (MVA) and stroke in NCCM patients (3,8-11). Moreover, *MYH7* variants are frequently identified in pediatric cardiomyopathies (12-16).

Additionally, variants in specific domains of *MYH7* have been associated to specific cardiomyopathies and prognosis. Structurally, MHC-β can be subdivided into three domains, i.e. subfragment-1 (amino acids 1-847), subfragment-2 (848-1216) and light meromyosin (1217-1935) (17). Alternatively, MHC-β can be divided into three functional regions, i.e. the motor (amino acids 1-778), lever (779-838) and tail (839-1935) (18). Parts of the MHC-β motor and lever regions are found to be enriched with variants causing HCM, particularly the converter (amino acids 707-774) and myosin binding protein C-binding regions (19-23). Moreover, variants in the motor region have been associated to worse outcome in HCM patients (17,21). Conversely, DCM- and NCCM-causing variants may be more common in the tail region and may confer worse prognosis in NCCM (7,20).

Previous studies mainly focused on one type of cardiomyopathy and either adult or

pediatric patients. Moreover, prognostic factors for disease development and subsequent events for at-risk family members remain unclear. Consequently, current guidelines for screening of at-risk family members do not differentiate between different genotypes (24-26). Therefore, we assessed the disease course of *MYH7* variant carriers, with a particular focus on early penetrance and clinical events, i.e. before the age of 12 years. Additionally, prognostic factors for penetrance and clinical outcomes were studied, including a family history of early penetrance or clinical events and variant location, to assess whether these could inform the prognosis of subsequent family members.

Methods

Subject inclusion

In this retrospective, multicenter cohort study, we included consecutive index patients, i.e. probands, and family members whom presented for genetic counselling at one of the participating centers and carried a (likely) pathogenic *MYH7* variant, according to classification guidelines at the time. Lists of carriers were extracted from the genome diagnostics laboratories. Additionally, pedigrees were assessed to include carriers that received counselling elsewhere, obligate carriers and first-degree family members with compatible phenotypes, i.e. HCM, DCM, NCCM or sudden cardiac death, who had not undergone genetic testing but were assumed to carry the familial *MYH7* variant. Subjects were sequenced at the University Medical Centre Utrecht between January 2006-December 2021, the Amsterdam University Medical Centre between April 2001-September 2021, and the University Medical Centre Groningen between August 2005-October 2021.

MYH7 variants were categorized as associated with HCM ($HCM_{variant}$), NCCM ($NCCM_{variant}$) or DCM ($DCM_{variant}$), in accordance with the predominantly observed phenotype in all carriers. Additionally, variants were divided into MHC-β domains, i.e. subfragment-1,

subfragment-2 and light meromyosin, as well as the motor, lever and tail, and specifically the converter region (17-19).

Variant pathogenicity was reassessed according to current guidelines (27,28). Subjects carrying *MYH7* variants reclassified as variant of unknown significance or (likely) benign were excluded, as well as compound heterozygous or homozygous subjects, and subjects carrying additional (likely) pathogenic variants in cardiomyopathy-associated genes.

The study was approved by the institutional review board of the UMC Utrecht and the need for informed consent was waived given the observational character and number of included subjects.

Data collection

Clinical data were obtained from electronic health records using a predefined, previously published Research Electronic Data Capture tool (Vanderbilt University, Nashville, TN, USA) (29). Phenotype-negative carriers were generally screened at intervals recommended by European guidelines and position statements, i.e. 1-2 year intervals in $HCM_{variant}$ carriers aged 10-20 years and 2-5 year intervals in $HCM_{variant}$ carriers aged ≥20 years, 1-3 year intervals in DCM- and $NCCM_{variant}$ carriers (24,25,30).

Study outcomes

HCM was defined as a maximum left ventricular wall thickness of ≥13 mm or with a z-score >2 in children, not explained by other causes (24). Z-scores were calculated according to Pettersen et al. (2008) (31). NCCM was defined as left ventricular non-compaction in accordance with the Jenni or Petersen criteria and a left ventricular ejection fraction (LVEF) <50%, not explained by coronary artery disease or abnormal loading conditions (32,33). The LVEF criterium was added to avoid overdiagnosis of non-compaction occurring as a physiological adaptation

without impacting prognosis (34,35). DCM was defined as left ventricular dilation and a LVEF <45%, not explained by coronary artery disease or abnormal loading conditions (30). Subjects fulfilling criteria for DCM but with (prior) left ventricular hypertrophy fulfilling HCM criteria or non-compaction fulfilling NCCM criteria were classified as HCM and NCCM, respectively.

Subjects with LVEF <50% but no other criteria for a specific cardiomyopathy diagnosis were classified as cardiomyopathy-not otherwise specified. Subjects suffering sudden cardiac death without information regarding the underlying phenotype were classified as sudden cardiac death-not otherwise specified.

Sudden cardiac death was defined as mortality resulting from documented MVA or occurring suddenly, i.e. with symptoms lasting <1 hour, in absence of other potential causes. MVA was defined as sustained ventricular tachycardia, i.e. ≥30 seconds in duration, resulting in hemodynamic instability and/or requiring termination, ventricular fibrillation, appropriate implantable cardioverter defibrillator therapy and/or (resuscitated) cardiac arrest.

Penetrance was defined as a clinical diagnosis fulfilling any of the above definitions. Additionally, as a more objective outcome, a composite endpoint of major cardiomyopathy-related events (MCE) was used, constituted of heart failure-events, MVA including sudden cardiac death, and septal reduction therapy, i.e. myectomy or alcohol septal ablation. Heart failure-events included heart failure-related hospitalization, left ventricular assist device implantation, heart transplantation and heart failure-related mortality. A secondary endpoint of cardiovascular mortality and surrogates was constituted of left ventricular assist device implantation, heart transplantation, heart-failure related mortality, MVA and sudden cardiac death.

Statistical analyses

Categorical data were expressed as counts with percentages and assessed using χ^2 (or

Fisher-Freeman-Halton's exact test if cell counts were expected <5 or observed <10). Continuous data were expressed as means with standard deviations or median with interquartile ranges depending on their distribution, and assessed using independent samples t-test or Mann–Whitney U test accordingly.

To assess whether a family history of early penetrance or early MCE, assessed as separate variables, could inform the prognosis of subsequent family members, the first subjects to present with early penetrance and and/or early MCE were identified in each family and subsequently presenting family members were designated as exposed.

Disease course was assessed using Kaplan-Meier curves and log-rank tests for both index patients and family members. Event rates were calculated with exact 95% confidence intervals. Prognostic factors were assessed using Cox regression. Time-dependent predictor variables were identified using Schoenfeld residuals and modelled using time interval-specific coefficients. In multivariable analysis, stepwise backward selection was performed using Akaike's Information Criterion.

Sensitivity analyses were performed, restricted to subjects whom underwent genetic testing, $HCM_{variant}$ and $NCCM_{variant}$/$DCM_{variant}$ carriers separately, and family members. Additionally, to assess effects of large families, sensitivity analyses restricted to families with <10 subjects were performed. P-values <0.05 were considered statistically significant.

Results

In total, 581 subjects were included, with 30.1% index patients, 48.4% male and median age at first presentation 37.0 years (interquartile range 19.5-50.2). A flowchart of subject inclusion is provided in Figure 1. A total of 74 distinct (likely) pathogenic *MYH7* variants were identified, including 49 categorized as $HCM_{variant}$, 12 as $NCCM_{variant}$ and 13 as

$DCM_{variant}$. Figure 2 shows the distribution of variants across MHC-β. Detailed information on the *MYH7* variants, numbers of subjects and associated phenotypes is provided in Supplemental Table 1.

Data on baseline characteristics were available for 540 subjects (92.9%) and are provided in Table 1. Additionally, Supplemental Table 2 provides baseline characteristics including z-scores for the 101 subjects (18.7%) that presented at ages <16 years. Subjects were followed for a median of 5.2 years (interquartile range 0.34-12).

Cardiomyopathy penetrance

Data regarding the presence of phenotypes at baseline were available for 513 subjects (88.3%). At baseline, 296 subjects (57.7%) were diagnosed with a phenotype, including 193 $HCM_{variant}$ carriers (median age 42.9 years, interquartile range 26.8-55.7), 50 $NCCM_{variant}$ carriers (median age 27.0 years, interquartile range 0.5-43.7) and 53 $DCM_{variant}$ carriers (median age 35.0 years, interquartile range 11.4-50.0). The remaining 217 subjects (42.3%) were phenotype-negative (median age 39.0 years, interquartile range 22.2-52.7). During a median follow-up of 3.4 years (interquartile range 0.0-7.8), penetrance was observed in 46 initially phenotype-negative subjects (21.2%), at rates of 3.4/100 person-years for $HCM_{variant}$ carriers, 8.0/100 person-years for $NCCM_{variant}$ carriers and 4.1/100 person-years for $DCM_{variant}$ carriers (log-rank p=0.003). Kaplan-Meier curves are provided in Supplemental Figure 1.

There were significant differences in penetrance (p=0.017), driven by differences among family members, as shown in the Kaplan-Meier curves in Figure 3 and the corresponding event rates in Table 2. Among family members, penetrance occurred earlier in $NCCM_{variant}$ carriers (median age 33.8 years, 95% confidence interval 25.7-57.8) compared to $HCM_{variant}$ (median age 55.9, 95% confidence interval 52.8-63.5, p<0.001) and $DCM_{variant}$ carriers (median age 50.4, 95%

confidence interval 44.0-67.8, p=0.009). Supplemental Table 3 provides further p-values for pairwise comparisons.

Early penetrance was significantly more frequent in $NCCM_{variant}$ carriers (21.2%) and $DCM_{variant}$ (15.3%) compared to $HCM_{variant}$ carriers (2.9%; log-rank p<0.001 overall and for both comparisons). Differences in the occurrence of early penetrance persisted in index patients (overall p=0.004; $HCM_{variant}$ versus $DCM_{variant}$ p<0.001) and family members (overall p<0.001; $HCM_{variant}$ versus $NCCM_{variant}$ and versus $DCM_{variant}$ p<0.001).

Clinical outcome

Data on MCE were available for 579 subjects (99.6%). As shown in Table 2, a total of 75 index patients (43.4%) and 68 family members (16.8%) experienced MCE, including 92/386 $HCM_{variant}$ (23.8%), 18/83 $NCCM_{variant}$ (21.7%) and 33/110 $DCM_{variant}$ carriers (30.0%).

Figure 4 shows Kaplan-Meier curves for MCE. Risk of MCE differed significantly in index patients (p<0.001), with $DCM_{variant}$ carriers having a significantly higher risk of MCE compared to $HCM_{variant}$ carriers (p<0.001). Among family members, no overall differences in risk of MCE were observed (overall p=0.291). As shown in Supplemental Figure 2, these findings persisted when the outcome was restricted to cardiovascular mortality and surrogates.

Early MCE was significantly more common in $NCCM_{variant}$ (12.0%) and $DCM_{variant}$ carriers (10.0%), compared to $HCM_{variant}$ carriers (2.1%; log-rank p<0.001 for both comparisons). Differences in the occurrence of early MCE persisted among index patients ($HCM_{variant}$ versus $DCM_{variant}$ p<0.001) and family members ($HCM_{variant}$ versus $NCCM_{variant}$ p<0.001 and versus $DCM_{variant}$ p=0.004).

Heart failure-events predominated among $NCCM_{variant}$ and $DCM_{variant}$ carriers, frequently occurring at ages <12 years (10/15 heart failure-events in $NCCM_{variant}$ carriers and 11/28 in

$DCM_{variant}$ carriers). All early heart-failure events in $NCCM_{variant}$ and 8/11 in $DCM_{variant}$ carriers occurred at an age <1 year.

Prognostic factors for penetrance and major cardiomyopathy-related events

Figure 5 shows the results from Cox regression for penetrance. The hazards of carrying a $NCCM_{variant}/DCM_{variant}$, family history of early penetrance and family history of early MCE were significantly non-proportional (Schoenfeld test p<0.001, 0.001 and <0.001 in univariable analysis, respectively). This was resolved by modelling these variables across age periods ≤1, 1-12 and >12 years. In univariable analysis, risk of penetrance was significantly increased in variants located in the MHC-β motor and specifically the converter region, and at ages ≤1 year in $NCCM_{variant}/DCM_{variant}$ carriers and subjects with a family history of early penetrance or MCE. In multivariable analysis, the variables sex, index patient, $NCCM_{variant}/DCM_{variant}$, variant location in the converter region and family history of early MCE were selected. Except for sex, all achieved statistical significance.

Figure 6 shows the results from Cox regression for MCE. The hazard of carrying a $NCCM_{variant}/DCM_{variant}$ was significantly non-proportional (Schoenfeld test p=0.042). This variable was modelled across two age periods, i.e. ≤5 and >5 years. In univariable analysis, risk of MCE was significantly increased in index patients and at ages ≤5 years in $NCCM_{variant}/DCM_{variant}$ carriers. Both of these and family history of early MCE were selected in multivariable analysis, with all three variables attaining statistical significance.

Sensitivity analyses

Baseline characteristics restricted to subjects that underwent genetic testing, family members and families with <10 subjects are provided in Tables S4-6. Results of the sensitivity analyses are provided in Supplemental Figure 3 for penetrance and Supplemental Figure 4 for

MCE.

Point estimates generally remained similarly directed. However, the increased risk of penetrance for the converter region was limited to $HCM_{variant}$ carriers as only one $NCCM_{variant}/DCM_{variant}$ carrier with a variant in the converter region was identified. Variant location in the MHC-β tail did not predict penetrance or MCE in $NCCM_{variant}/DCM_{variant}$ carriers either (adjusted hazard ratio [95% confidence interval]: 1.10 [0.74-1.3], p=0.644, and 1.62 [0.89-2.96], p=0.117, respectively). Additionally, a family history of MCE did not appear to increase risk of MCE in $NCCM_{variant}/DCM_{variant}$ carriers.

Discussion

In this retrospective cohort study, we assessed the disease course and prognostic risk factors in carriers of (likely) pathogenic *MYH7* variants. Early penetrance and MCE were common among $NCCM_{variant}$ and $DCM_{variant}$ carriers. Associated phenotype, variant localization in the MHC-β converter region, and a family history of early MCE were identified as prognostic factors for penetrance. Additionally, associated phenotype and a family history of early MCE predicted MCE.

Early penetrance & MCE

Several studies indicated a high prevalence of *MYH7* variants among pediatric cardiomyopathy patients (12-15). In HCM, *MYH7* variants convey worse prognosis, particularly compared to *MYBPC3* variant carriers (3,9). Additionally, *MYH7* variants predicted early penetrance and MCE in a study assessing children referred for predictive screening for HCM (10). In a recent study on DCM-associated *MYH7* variants (including patients fulfilling NCCM criteria), a relatively high percentage of carriers presented with DCM during the first year of life, but subsequent prognosis was similar to *TTN* variant carriers and better than in *LMNA* variant carriers

(8). In NCCM, one study indicated a relatively benign prognosis for *MYH7* variants (11). We show that among *MYH7* variant carriers, a high proportion of $NCCM_{variant}$ and $DCM_{variant}$ carriers, both index patients and family members, experienced penetrance and MCE before the age of 12 years, particularly clustering around birth. In comparison, the incidence of early penetrance and MCE among $HCM_{variant}$ carriers is relatively low. However, when HCM did occur at an early age, it was frequently complicated by MCE, in line with a recent study showing worse outcome for patients with HCM diagnosed before the age of 18 (12).

Identification of subjects with early penetrance may allow timely treatment. Treatment of asymptomatic pediatric NCCM and DCM with heart failure medication may slow progression and potentially regress the phenotype (36,37). In HCM, there are currently no treatments proven to slow or revert progression, but the results of trials involving valsartan and mavacamten seem promising (38-40).

Additionally, identification of subjects with early penetrance allows risk stratification. Two specific risk calculators for MVA in pediatric HCM patients have been developed and externally validated: HCM Risk-Kids and PRIMaCY (41-43). Genetic variables were only included in an ancillary model in the PRIMaCY study with the addition of pathogenic variants in any gene, but only marginally improved model performance (43). *MYH7* was not included as a predictor in the model, and no genotype-specific sensitivity analyses were performed. As heart failure may constitute a competing risk in *MYH7* variant carriers, the performance of these models in HCM patients carrying *MYH7* variants may require further investigation.

In a recently published expert consensus statement on genetic testing for cardiac diseases, screening for both HCM and DCM is recommended in relatives aged ≥10-12 years; testing at a younger age may be considered, especially when there is a family history of early-onset disease

(26). Conversely, the 2018 Heart Failure Society of America Practice Guideline recommends screening from any age for family members at risk for HCM or DCM (44). Neither document provides genotype-specific recommendations. Based on our results, initiation of screening at an early age can be considered in relatives of $NCCM_{variant}$ and $DCM_{variant}$ carrying patients. As many events occur at ages <1 year, neonatal (or prenatal) screening may even be considered.

Prognostic factors: family history and *MYH7* variant location

A family history of early MCE predicted penetrance and MCE in our study. A similar finding was reported in a previous study in children undergoing family screening for HCM, where children diagnosed with HCM more frequently had a family history of childhood HCM (45). In our study, a family history of early MCE remained predictive of both penetrance and MCE in sensitivity analyses restricted to $HCM_{variant}$ carriers, but only predicted penetrance among $NCCM_{variant}$/$DCM_{variant}$ carriers. Although a family history of early penetrance or MCE may have influenced referral of family members resulting in earlier diagnosis, it is unlikely to have influenced the occurrence of MCE. Therefore, this finding likely demonstrates the presence of additional genetic and/or shared environmental factors and can be used to guide screening strategies, particularly in $HCM_{variant}$ carriers.

Previous studies observed worse prognosis in HCM patients carrying variants in the motor region, particularly in the converter region (17,21). This region connects the MHC-β head to the lever, and plays a key role in MHC-β elasticity during actin-myosin cross-bridge cycling (19,46). Likewise, our study showed an increased risk of penetrance for converter region variants in $HCM_{variant}$ carriers. Consequently, earlier screening may be considered in family members of patients carrying a converter region $HCM_{variant}$.

In a recent study on patients carrying *MYH7* variants associated with DCM, including

patients fulfilling NCCM criteria, variant location did not appear to influence prognosis (8). Among patients with NCCM, variants located in the MHC-β tail have previously been associated to NCCM with LV dilatation fulfilling DCM criteria (7). In our study, variant location in the MHC-β tail did not appear to increase risk of penetrance or MCE in $DCM_{variant}$/$NCCM_{variant}$ carriers.

Strengths & limitations

To our knowledge, our study constitutes the largest cohort of *MYH7* variant carriers to date, which allowed for thorough assessment of carriers' prognoses across different phenotypes. Strengths of our study are the genotype-driven inclusion and the inclusion of many family members, allowing analyses specifically in this subgroup with lower event rates. Additionally, we performed a systematic reclassification of *MYH7* variants according to international criteria, reclassifying a relatively high proportion of variants (14.9%) as variants of unknown significance.

There are, however, several limitations to our study. The retrospective design of this study inherently results in ascertainment bias, referral bias and missing data. Ascertainment and referral biases were limited by selecting subjects based on genotype rather than phenotype. As our results remained robust in analyses restricted to family members, these biases are likely limited. Missing data was pervasive in baseline electrocardiographic and echocardiographic parameters, but was mostly absent in the predictor variables evaluated in this study. Of note, follow-up was limited in a notable part of our cohort, which restricted us in making any recommendations regarding follow-up intervals.

Use of age as the time variable in survival analyses allowed us to assess prognosis throughout life and identify prognostic factors to guide the decision for earlier screening. However, this precluded assessment of parameters only measured at a certain point in life, e.g. maximum wall thickness and LVEF, which should be assessed in prognostic studies evaluating risk

stratification models. Additionally, we deemed a composite endpoint of heart failure events, MVA and septal reduction therapy most appropriate for assessing at which age screening should be initiated. However, for specific interventions, use of stricter, specific endpoints may be more appropriate, with consideration for competing risks.

Variant classifications are tentative. As DCM patients were not systematically evaluated with cardiac MRI, non-compaction may not have been detected in some patients (47). Since this is a historical cohort, Next Generation Sequencing panels were only performed in 88 index patients (50.6%) and 22 family members (6.0%). Finally, as the Dutch population is of majority (white) Western European descent, our results may not be generalizable to populations with other ethnic compositions.

Conclusion

MYH7 variants can cause cardiomyopathies and MCE from at a young age. Screening at younger ages may be warranted, particularly in carriers of NCCM- or DCM-associated variants and/or with a family history of MCE at <12 years.

Clinical perspectives

Competency in Medical Knowledge: *MYH7* variants can cause cardiomyopathies at a young age. Early penetrance and major cardiomyopathy-related events (MCE) are particularly common in NCCM- and DCM-associated variants. A family history of early MCE predicts both penetrance and MCE, particularly in HCM-associated variants. HCM-associated *MYH7* variants located in the converter region are associated with an increased risk of penetrance.

Competency in Patient Care: A detailed family history including occurrence of early MCE should be obtained in *MYH7* variant carriers, as this predicts penetrance and MCE. Earlier screening of relatives may be considered in families with *MYH7*-associated DCM/NCCM.

Translational Outlook: The results of this study may improve future individualized risk stratification in *MYH7* variant carriers.

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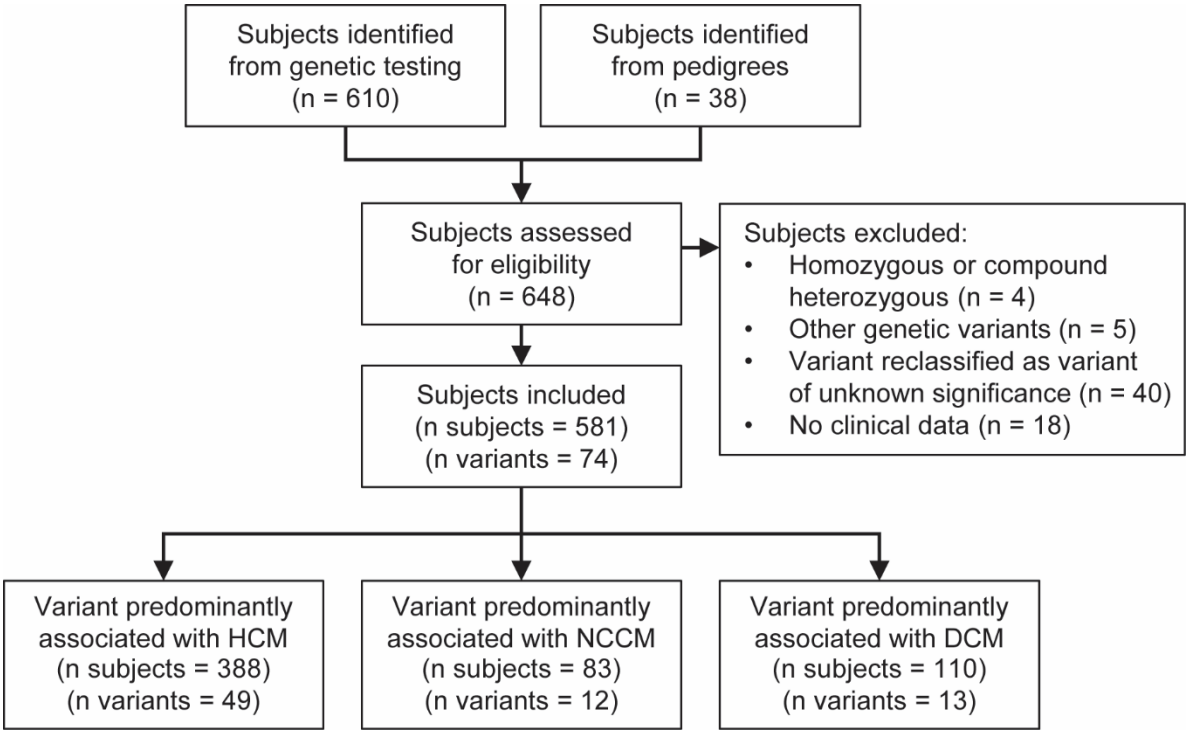
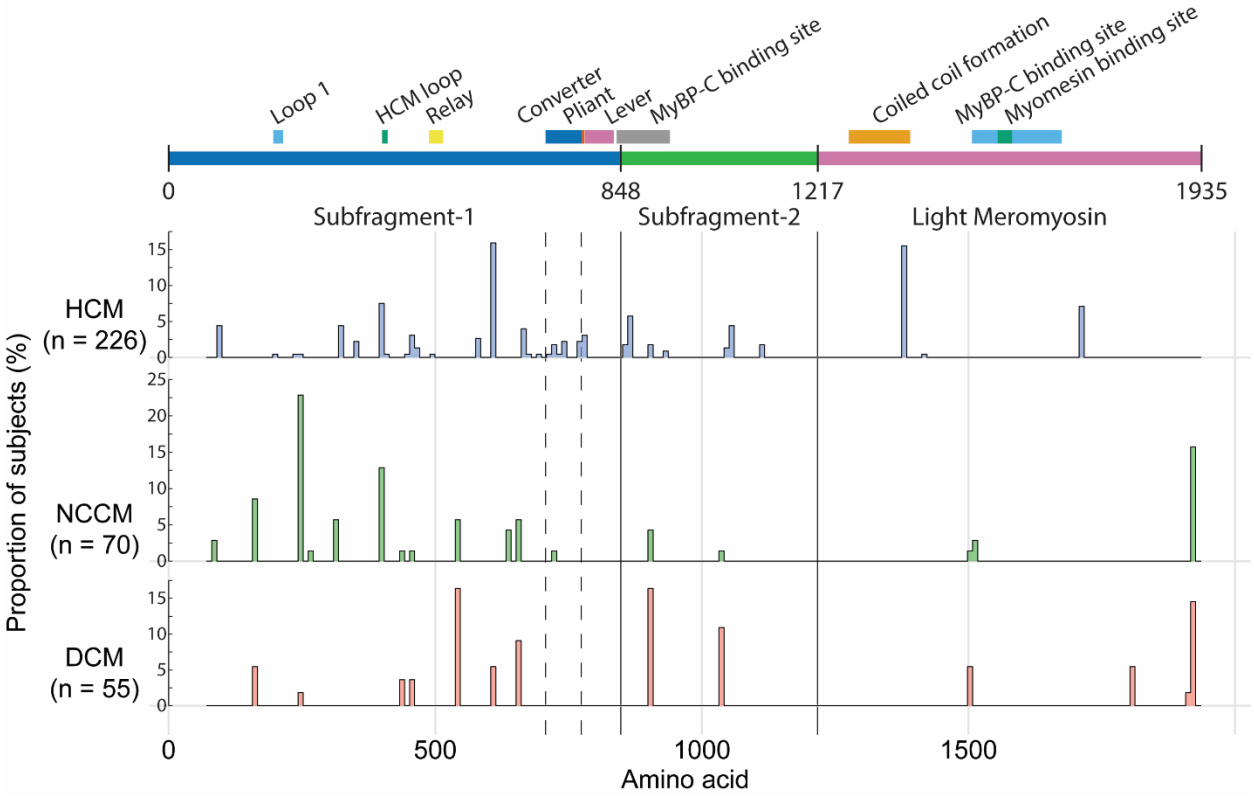
Figures with figure legends

Figure 1. Subject inclusion



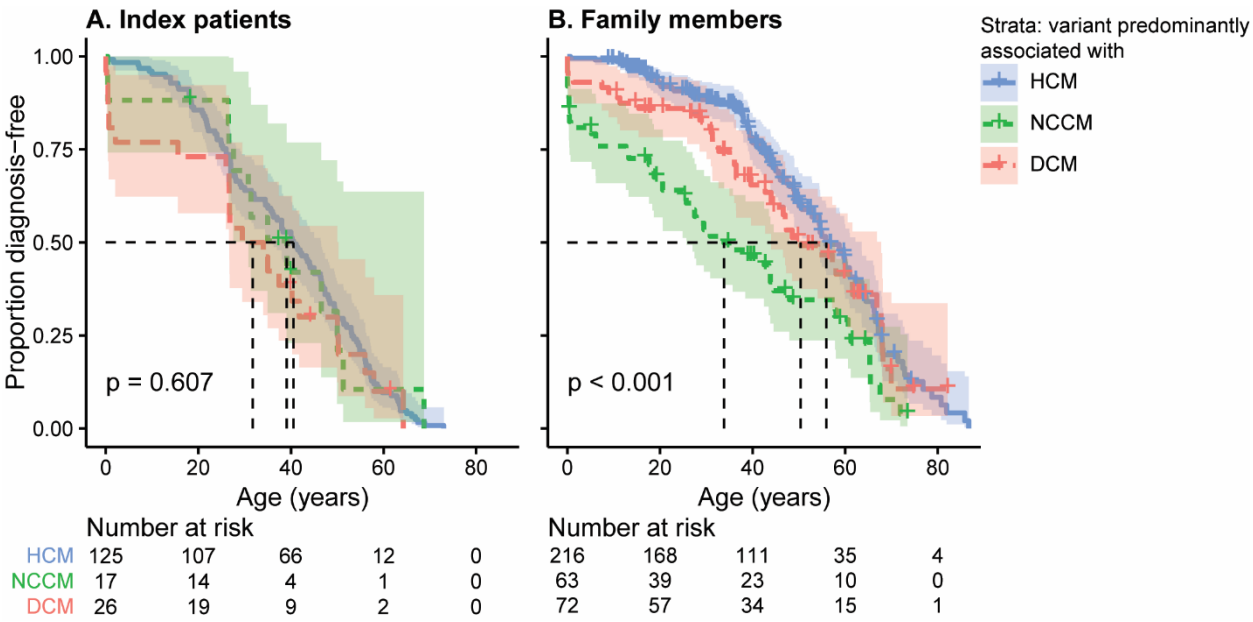
Flowchart depicting subject inclusion. Subjects were classified according to the predominant cardiomyopathy associated to each *MYH7* variant. DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NCCM, non-compaction cardiomyopathy.

Figure 2. Distribution of *MYH7* variants



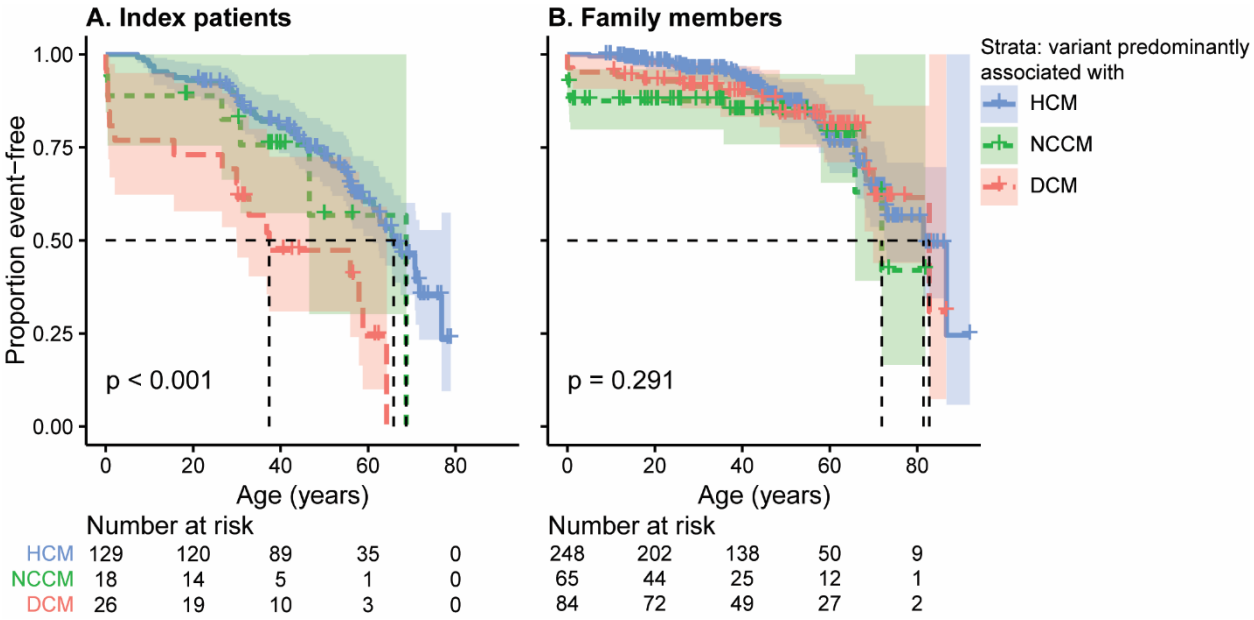
Schematic representation of myosin heavy chain beta with the distribution of variants in subjects with HCM, NCCM and DCM. Variants were grouped per 10 amino acids. Solid lines delineate subfragment borders, and dashed lines the converter region. MyBP-C, myosin-binding protein-C; other abbreviations as in Figure 1.

Figure 3. Penetrance



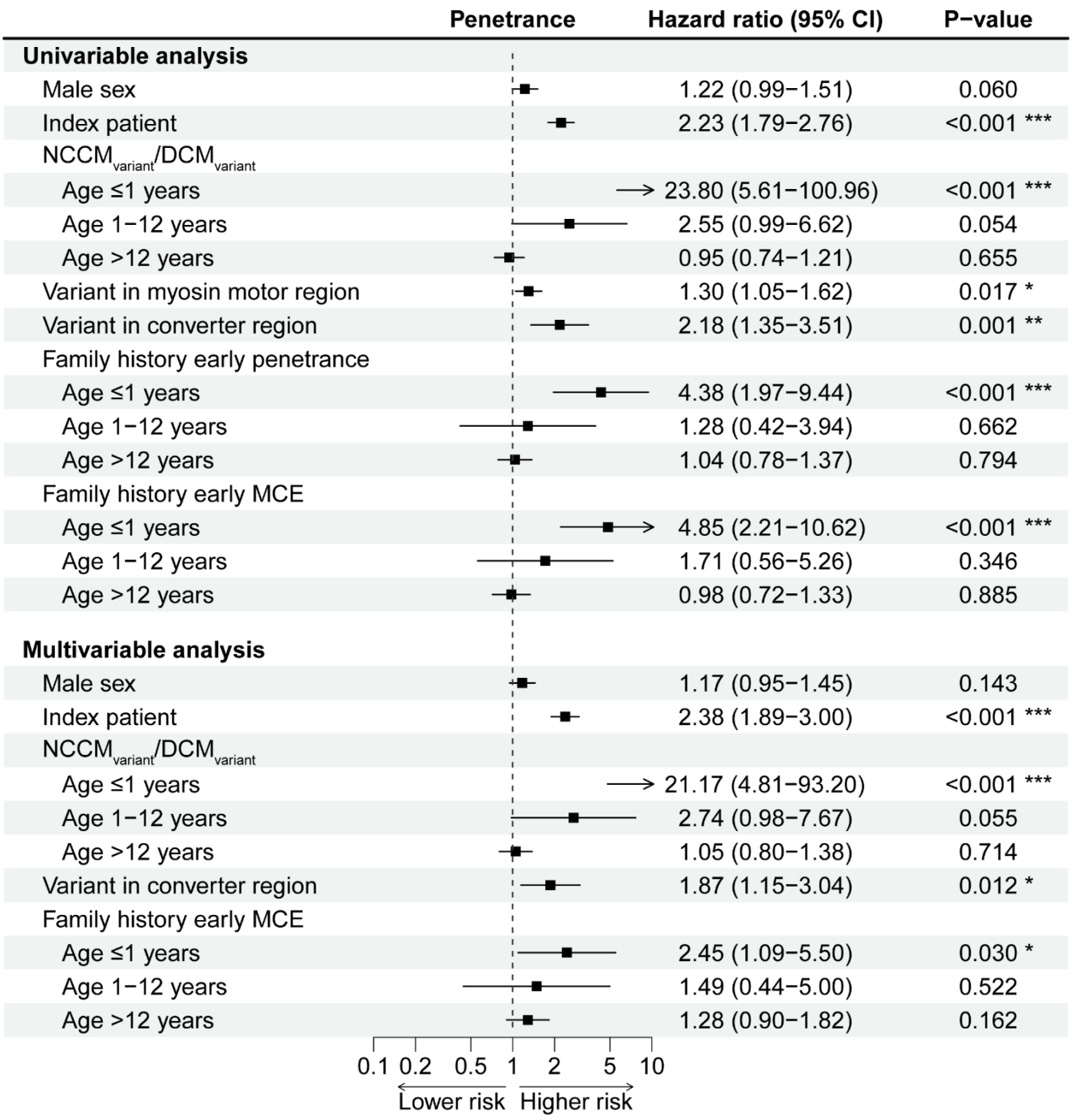
Kaplan-Meier curves of age at diagnosis with 95% confidence intervals, stratified by the predominant cardiomyopathy associated with each *MYH7* variant, for index patients (A) and family members (B). Dashed lines indicate median diagnosis-free survival. Abbreviations as in Figure 1.

Figure 4. Major cardiomyopathy-related events



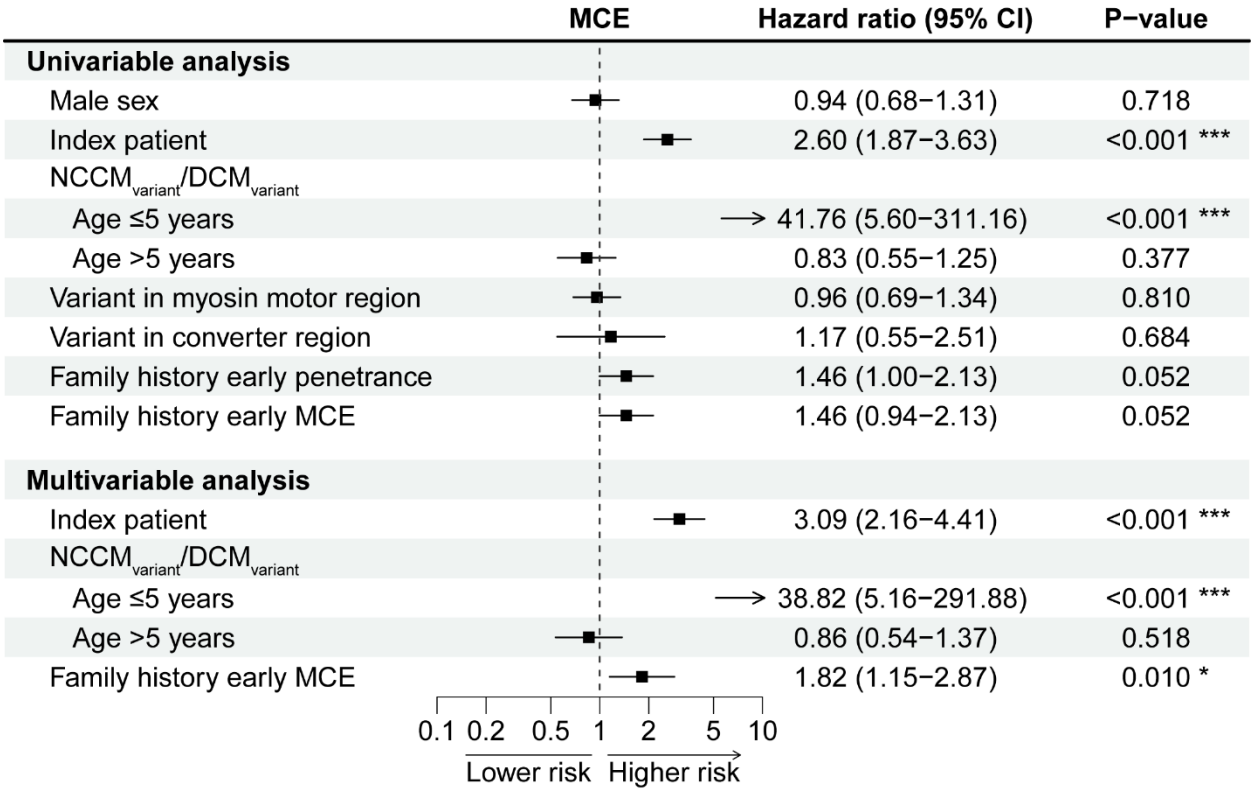
Kaplan-Meier curves of age at major cardiomyopathy-related events with 95% confidence intervals, stratified by the predominant cardiomyopathy associated with each *MYH7* variant, for index patients (A) and family members (B). Dashed lines indicate median event-free survival. Abbreviations as in Figure 1.

Figure 5. Prognostic factors for penetrance



Forest plots of the results of Cox regression for penetrance. *p<0.05; **p<0.01; ***p<0.001. CI, confidence interval; MCE, major cardiomyopathy-related events; $NCCM_{variant}/DCM_{variant}$, predominantly non-compaction/dilated cardiomyopathy-associated variant.

Figure 6. Prognostic factors for major cardiomyopathy-related events



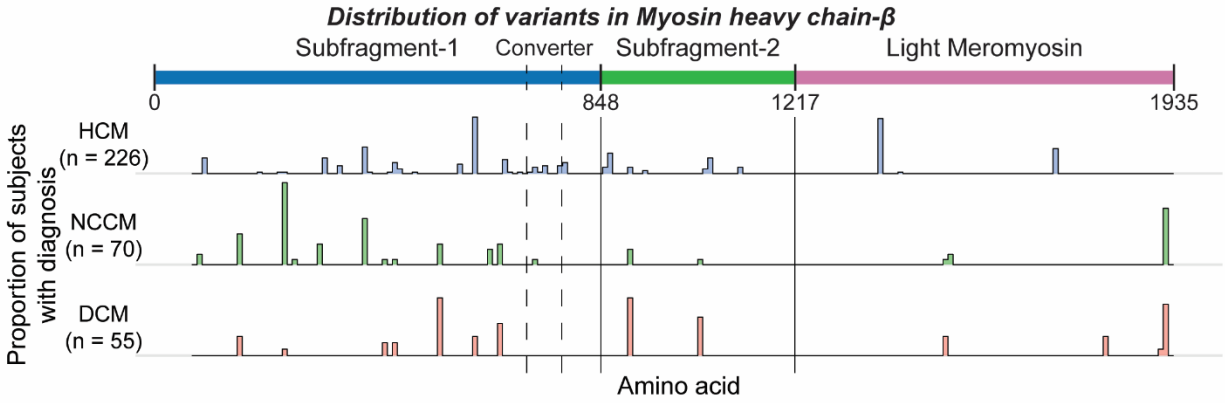
Forest plots of the results of Cox regression for major cardiomyopathy-related events. *p<0.05; ***p<0.001. Abbreviations as in Figure 5.

Central illustration

Penetrance and prognosis of *MYH7* variant-associated cardiomyopathies: Results from a Dutch multicenter cohort study

581 subjects, follow-up 5.2 years (IQR 0.34-12)
- 359 with penetrance (44 at age <12 years)
- 143 with major cardiomyopathy-related events (29 at age <12 years)

74 distinct (likely) pathogenic *MYH7* variants
- 49 predominantly HCM-associated
- 12 predominantly NCCM-associated
- 13 predominantly DCM-associated



Penetrance

Index patients
- No overall difference between HCM-, NCCM- and DCM-associated variants (p=0.607)
- Higher proportion before age 12 in DCM- (23.1%) compared to HCM-associated variants (4.8%, p<0.001)

Family members
- Higher risk in NCCM- compared to HCM- (p<0.001) and DCM-associated variants (p=0.009)
- Higher proportion before age 12 in NCCM- (23.8%) and DCM- (12.5%) compared to HCM-associated variants (1.9%, p<0.001 for both comparisons)

Prognostic factors	Adjusted HR (95% CI)	P−value
$NCCM_{variant}/DCM_{variant}$, at age ≤1 years	21.17 (4.81−93.20)	<0.001 ***
Variant in converter region (HCM)	1.87 (1.15−3.04)	0.012 *
Family history early MCE, at age ≤1 years	2.45 (1.09−5.50)	0.030 *

Major cardiomyopathy-related events

Index patients
- Higher overall risk in DCM- compared to HCM-associated variants (p<0.001)
- Higher proportion before age 12 in DCM- (23.1%) compared to HCM-associated variants (4.7%, p<0.001)

Family members
- No overall difference between HCM-, NCCM- and DCM-associated variants (p=0.291)
- Higher proportion before age 12 in NCCM- (12.3%) and DCM- (6.0%) compared to HCM-associated variants (0.8%, p<0.001 and p=0.004, respectively)

Prognostic factors	Adjusted HR (95% CI)	P−value
$NCCM_{variant}/DCM_{variant}$, at age ≤5 years	38.82 (5.16−291.88)	<0.001 ***
Family history early MCE	1.82 (1.15−2.87)	0.010 *

Central illustration showing the main results. CI, confidence interval; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; MCE, major cardiomyopathy-related events; NCCM, non-compaction cardiomyopathy.

Tables

Table 1. Baseline characteristics

		$HCM_{variant}$ (n = 350)	$NCCM_{variant}$ (n = 82)	$DCM_{variant}$ (n = 108)	P-value
Age (years)		38.2 [21.8, 51.4]	29.8 [7.40, 44.4]	36.8 [18.7, 54.3]	**0.005**
Male sex		194 (50.0)	31 (37.3)	56 (50.9)	0.094
Body surface area (m^2)		1.8 [1.7, 2.0]	1.8 [1.7, 2.0]	1.8 [1.4, 2.0]	0.327
Index patient		130 (33.7)	18 (21.7)	26 (23.6)	**0.026**
MHC-β domain	Subfragment-1	235 (60.6)	61 (73.5)	61 (55.5)	**<0.001**
	Subfragment-2	61 (15.7)	0 (0.0)	20 (18.2)	
	Light meromyosin	92 (23.7)	22 (26.5)	29 (26.4)	
	Motor	235 (60.6)	61 (73.5)	61 (55.5)	**0.030**
	Lever	0 (0.0)	0 (0.0)	0 (0.0)	
	Tail	153 (39.4)	22 (26.5)	49 (44.5)	
	Converter region	27 (7.0)	1 (1.2)	0 (0.0)	**0.001**
NYHA class III/IV		8 (2.8)	8 (11.0)	23 (25.6)	**<0.001**

LA diameter (mm)		37 (7)	35 (8)	38 (8)	0.389
Maximum wall thickness (mm)		13 [9, 18]	8 [7, 9]	8 [7, 9]	**<0.001**
LV ejection fraction (%)		60 [60, 60]	50 [45, 60]	50 [30, 60]	**<0.001**
LV end-diastolic diameter (mm)		43 [40, 47]	49 [43, 53]	54 [47, 62]	**<0.001**
Family history	Early penetrance	31 (8.0)	45 (54.2)	45 (40.9)	**<0.001**
	Early MCE	23 (5.9)	42 (50.6)	26 (23.6)	**<0.001**
Penetrance		193 (57.6)	50 (62.5)	53 (54.1)	0.527
Phenotype	HCM	186 (55.5)	0 (0.0)	0 (0.0)	
	NCCM	1 (0.3)	45 (56.2)	11 (11.2)	
	DCM	2 (0.6)	3 (3.8)	41 (41.8)	
	CMP-NOS	1 (0.3)	0 (0.0)	1 (1.0)	
	SCD-NOS	3 (0.9)	2 (2.5)	0 (0.0)	
	Phenotype-negative	142 (42.4)	30 (37.5)	45 (45.9)	

Subject characteristics at first presentation, stratified by the dominant phenotype associated with the carried *MYH7* variant. Data are presented as means (standard deviation), medians [interquartile range] or counts (percentage). P-values <0.05 are shown in bold. CMP-NOS, cardiomyopathy not otherwise specified; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV,

left ventricular; MCE, major cardiomyopathy-related event; MHC-β, myosin heavy chain beta; NCCM, non-compaction cardiomyopathy; NYHA, New York Heart Association; SCD-NOS, sudden cardiac death not otherwise specified.

Table 2. Outcomes

	Index patients				Family members			
	$HCM_{variant}$	**$NCCM_{variant}$**	**$DCM_{variant}$**	**P-value**	**$HCM_{variant}$**	**$NCCM_{variant}$**	**$DCM_{variant}$**	**P-value**
Penetrance (%)	126 (100.0)	13 (76.5)	23 (88.5)	0.607	107 (48.4)	46 (73.0)	44 (58.7)	**<0.001**
Rate per 100 PY (95% CI)	2.5 (2.1-3.0)	2.3 (1.2-3.9)	2.9 (1.8-4.3)		1.2 (1.0-1.4)	2.4 (1.8-3.2)	1.4 (1.0-2.0)	
At age <12 years (%)	6 (4.8)	2 (11.8)	6 (23.1)	**0.004**	4 (1.9)	15 (23.8)	9 (12.5)	**<0.001**
MCE (%)	52 (40.3)	6 (33.3)	17 (65.4)	**<0.001**	40 (15.7)	12 (18.5)	16 (19.0)	0.291
Rate per 100 PY (95% CI)	0.8 (0.6-1.1)	1.0 (0.4-2.1)	2.0 (1.2-3.2)		0.4 (0.3-0.5)	0.6 (0.3-1.0)	0.4 (0.2-0.7)	
At age <12 years (%)	6 (4.7)	2 (11.1)	6 (23.1)	**0.003**	2 (0.8)	8 (12.3)	5 (6.0)	**<0.001**
Cardiovascular mortality* (%)	24 (18.6)	2 (11.1)	9 (34.6)	**0.015**	28 (11.0)	10 (15.4)	12 (14.3)	0.200
Rate per 100 PY (95% CI)	0.4 (0.2-0.6)	0.3 (0.0-1.1)	0.9 (0.4-1.7)		0.3 (0.2-0.4)	0.5 (0.2-0.8)	0.3 (0.2-0.5)	
At age <12 years (%)	1 (0.8)	2 (11.1)	2 (7.7)	**0.010**	1 (0.4)	7 (10.8)	3 (3.6)	**<0.001**
Heart failure-events (%)	20 (15.5)	6 (33.3)	16 (61.5)	**<0.001**	15 (5.9)	9 (13.8)	12 (14.3)	**0.004**
Rate per 100 PY (95% CI)	0.3 (0.2-0.5)	1.0 (0.4-2.1)	1.1 (0.5-2.0)		0.1 (0.1-0.2)	0.4 (0.2-0.8)	0.3 (0.2-0.6)	
At age <12 years (%)	1 (0.8)	2 (11.1)	6 (23.1)	**<0.001**	0 (0.0)	8 (12.3)	5 (6.0)	**<0.001**
MVA (%)	18 (14.3)	0 (0.0)	5 (20.0)	0.084	19 (7.9)	4 (6.5)	5 (6.1)	0.651

Rate per 100 PY (95% CI)	0.3 (0.2-0.5)	0.5 (0.2-1.3)	0.2 (0.1-0.3)	0.2 (0.1-0.5)	0.1 (0.0-0.3)
At age <12 years (%)	1 (0.8)	0 (0.0)	1 (0.4)	1 (1.6)	0 (0.0)
SRT (%)	23 (18.3)		10 (4.1)		
Rate per 100 PY (95% CI)	0.4 (0.2-0.6)		0.1 (0.0-0.2)		
At age <12 years (%)	5 (4.0)		1 (0.4)		

Numbers of subjects experiencing events and corresponding event rates, stratified by to the predominant cardiomyopathy in each *MYH7* variant. P-values were obtained from log-rank tests. P-values <0.05 are shown in bold. *Including surrogates. CI, confidence interval; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; MCE, major cardiomyopathy-related events; MVA, malignant ventricular arrhythmia; NCCM, non-compaction cardiomyopathy; PY, person-years; SRT, septal reduction therapy.