Differences in Patient Characteristics and Burden of Disease in Adults with *MYBPC3*-Associated HCM

Wang W[1], Varfaj F[1], Robertson L[1], Harrison W[1], Haroldson J[1], Tingley W[1], Lakdawala N[2], Owens A[2], Saberi S[2], Lin K[2], Stendahl J[2], Parikh V[2], Ingles J[2], Ashley E[2], Ware J[2], Michels M[2], Lampert R[2], Abrams D[2], Rossano J[2], Russell M[2], Ryan T[2], Olivotto I[2], Day S[2], Ho C[2], Helms A[2]

[1]Tenaya Therapeutics, Inc. 171 Oyster Point Blvd, Suite 500, San Francisco, CA 94080 United States; [2]SHaRe Registry Research Member, the Sarcomeric Human Cardiomyopathy Registry

Contact email: wharrison@tenayathera.com

Background

Pathogenic variants in the myosin-binding protein C (*MYBPC3*) gene are the leading genetic cause of hypertrophic cardiomyopathy (HCM) resulting in reduced functional myosin-binding protein C (MyBP-C) levels. Studies have shown that adult patients with pathogenic sarcomere variant-HCM exhibit higher incidence of major clinical events than genotype-negative HCM patients. With the emergence of gene replacement therapies, characterizing the natural history of *MYBPC3*-asociated HCM is essential to inform future development of this class of targeted therapies.

Methods

- An analysis was conducted on adult *MYBPC3*-associated HCM patients enrolled in SHaRe (Sarcomeric Human Cardiomyopathy Registry) up to December 2024, based on primary diagnosis at ages of 18–39, 40–59, and ≥60 years, demographic & medical history at time of enrollment into SHaRe, and HCM-relevant outcomes since birth
- SHaRe is a multinational registry spanning 14 cardiac centers in US, EU and Australia.
- Group comparisons were conducted using ANOVA for continuous variables, Chi-square test for categorical variables, and the log-rank test for Kaplan-Meier curves.

Results

1,637 adults
MYBPC3-HCM patients

Cohort 1:	Cohort 2:	Cohort 3:
686 (41.9%) diagnosed at 18–39 y.o.	720 (44.0%) diagnosed at 40–59 y.o.	231 (14.1%) diagnosed at ≥60 y.o.

Baseline characteristics by Age at Diagnosis*	Cohort 1: 18–39 y.o.	Cohort 2: 40–59 y.o.	Cohort 3: ≥60 y.o.	p-value
Family history of HCM	67.3%	61.4%	63.6%	0.3761
Proband	78.9%	79.0%	68.4%	0.2403
Male, sex	67.5%	56.5%	42.0%	**<0.0001**
Duration of follow-up (years), mean (SD)	9.5 (8.9)	7.9 (7.2)	6.5 (7.4)	**<0.01**
Left ventricular maximal wall thickness (mm), mean (SD)	19.9 (6.1)	19.2 (5.2)	17.9 (4.4)	0.5271
Symptom burden (proportion of NYHA III/IV patients)	12.9%	10.3%	12.0%	0.4521
Atrial Fibrillation	10.9%	11.0%	15.6%	0.1599
Cardiac Arrest	2.0%	2.1%	0.9%	0.4714
ICD	18.7%	16.4%	12.1%	0.1051
Myectomy	4.4%	2.1%	0.4%	**<0.005**
Unexplained Syncope	8.2%	9.3%	9.5%	0.7218
Obstruction	22.9%	20.8%	22.5%	0.6989
Genotype				
1 *MYBPC3* P/LP/VUS	86.7%	85.4%	84.8%	0.6303
2+ *MYBPC3* P/LP/VUS	4.1%	3.3%	2.6%	
MYBPC3 + other SARC P/LP	1.5%	1.5%	1.3%	
MYBPC3 + other variants	7.7%	9.7%	11.3%	

* Percentages are based on available data for each variable, the denominator may differ from the total sample size due to missing values.

- Younger adults (18–39 y.o. cohort) had significantly greater septal reduction therapy than older cohorts (40–59 y.o. & ≥60 y.o.).

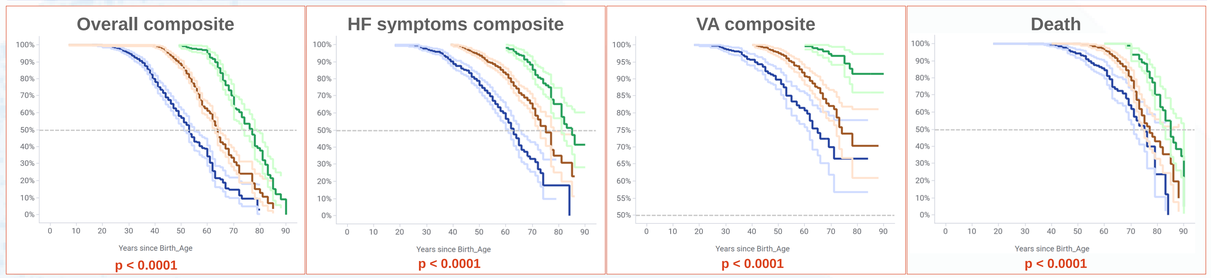
Prevalence of outcomes since birth	Cohort 1: 18–39 y.o.		Cohort 2: 40–59 y.o.		Cohort 3: ≥60 y.o.		p-value
Overall composite[1]	271 / 686	(39.5%)	316 / 720	(43.9%)	120 / 231	(51.9%)	**0.0420**
Heart failure (HF) symptoms composite[2]	179 / 686	(26.1%)	167 / 720	(23.2%)	61 / 231	(26.4%)	0.4854
Ventricular arrhythmia composite[3]	85 / 686	(12.4%)	81 / 720	(11.3%)	16 / 231	(6.9%)	0.0972
Death	69 / 686	(10.1%)	87 / 720	(12.1%)	52 / 231	(22.5%)	**<0.0001**
Sudden cardiac death	19 / 69	(27.5%)	13 / 87	(14.9%)	6 / 52	(11.5%)	**<0.0001**

Prevalence of outcomes since birth	Cohort 1: 18–39 y.o.		Cohort 2: 40–59 y.o.		Cohort 3: ≥60 y.o.		p-value
Cardiac arrest	34 / 686	(5.0%)	36 / 720	(5.0%)	4 / 231	(1.7%)	0.0988
Implantable cardioverter-defibrillator (ICD)	318 / 686	(46.4%)	284 / 720	(39.4%)	59 / 231	(25.5%)	**<0.0001**
ICD appropriate therapy	57 / 318	(17.9%)	54 / 284	(19.0%)	7 / 59	(11.9%)	0.4964
Atrial fibrillation	157 / 686	(22.9%)	209 / 720	(29.0%)	79 / 231	(34.2%)	**0.0077**
Cerebral vascular accident (CVA)	34 / 683	(5.0%)	55 / 720	(7.6%)	25 / 230	(10.9%)	**0.0093**
Unexplained syncope	115 / 686	(16.8%)	131 / 720	(18.2%)	36 / 231	(15.6%)	0.6576
Ventricular tachycardia/ventricular fibrillation (VT/VF)	46 / 551	(8.3%)	43 / 567	(7.6%)	13 / 182	(7.1%)	0.8429
Transplant/left ventricular assist device (LVAD)	20 / 686	(2.9%)	7 / 720	(1.0%)	0 / 231	(0%)	**0.0019**
Listed for transplant	4 / 498	(0.8%)	1 / 539	(0.2%)	0 / 154	(0%)	0.2126
Septal reduction therapy	154 / 686	(22.4%)	122 / 720	(16.9%)	16 / 231	(6.9%)	**<0.0001**
Hospitalization associated with HF	33 / 470	(7.0%)	21 / 479	(4.4%)	11 / 155	(7.1%)	0.1969

1. Overall Composite: NYHA III/IV OR Transplant OR VAD, OR Ventricular Arrhythmia Composite, OR Afib, OR Stroke, OR Death. **2.** HF Symptoms Composite: LVEF < 35% OR NYHA III/IV, OR Listed for Transplant, OR LVAD, OR Transplant, OR Hospitalized for HF, OR inotropes, OR myosin inhibitors, or loop diuretics. **3.** Ventricular Arrhythmia Composite: SCD OR Cardiac Arrest OR ICD Appropriate Firing

- Adult *MYBPC3*–associated HCM patients experience serious outcomes, including overall composite (43.2%), heart failure symptoms composite (24.9%), ventricular arrhythmia composite (11.1%), atrial fibrillation (27.2%), and death (12.7%) across the 3 adult cohorts.
- Roughly 50% of adult patients diagnosed before the age of 40 experience a serious cardiac event by the age of 50. This cohort had the highest prevalence of sudden cardiac death, ICD, and need for transplant or LVAD and septal reduction therapy.
  - Data suggests a trend towards a higher prevalence of VA composite in the youngest cohort, though this did not reach statistical significance (p = 0.0972), likely due to small sample size.
- In the oldest cohort, the prevalence of overall composite outcomes, death, AF, and CVA was highest (all p < 0.05), while the incidence of cardiac arrest was the lowest but did not reach statistical significance (p = 0.0988).

HCM outcome – Time to Event since birth



● Cohort 1: 18–39 y.o. ● Cohort 2: 40–59 y.o. ● Cohort 3: ≥60 y.o.

- Kaplan-Meier curves show a statistically significant, age-correlated difference in time to event for the overall composite, heart failure symptoms composite, ventricular arrhythmia composite, and death.

Conclusions

- **Adult *MYBPC3*-associated HCM patients of all ages are at risk for serious clinical manifestations including heart failure, arrhythmias, and sudden cardiac death.**
- **These findings underscore the importance of genetic diagnosis early and development of targeted therapies to restore MyBP-C levels, which could potentially modify the natural history of the disease.**

Contact information

Tenaya Therapeutics, Inc | Patient inquiries : patient.advocacy@tenayathera.com or clinical.trials@tenayathera.com