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, Saberi S[2], Lin K[2], Stendahl J[2], Parikh V, 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, 171 Oyster Point Blvd, Suite 500, San Francisco, CA 94080 United States; [2]SHaRe Registry Research Member, the Sarcomeric Human Cardiomyopathy Registry
Contact email: wwang@tenayathera.com

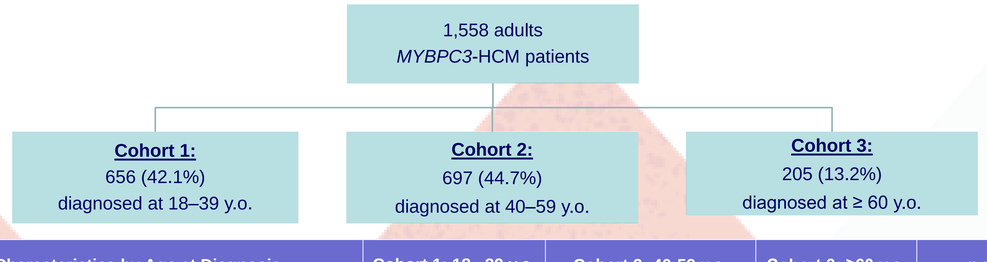
Background

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 all adult *MYBPC3*-associated HCM patients enrolled in SHaRe (Sarcomeric Human Cardiomyopathy Registry) up to Q1 2024, based on their primary diagnosis at the age of 18-39, 40-59, and ≥60 years.
- SHaRe is a multinational registry spanning 12 cardiac centers in US, EU and Australia.
- Group comparisons were conducted using Z-tests for continuous variables, Fisher's exact test for categorical variables,, and the log-rank test for Kaplan-Meier curves.

Results



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	68.3%	61.4%	62.9%	**<0.05**
Proband	79.3%	78.8%	68.6%	**<0.01**
Male, sex	66.8%	56.5%	41.0%	**<0.05**
Duration of follow-up, mean (SD)	9.8 (9.0)	7.8 (7.3)	6.1 (6.6)	**< 0.001**
Median left ventricular maximal wall thickness	20.1mm	19.4mm	18.0mm	**<0.05**
Symptom burden (proportion of NYHA III/IV patients)	14.2%	10.6%	11.5%	**<0.05**
Atrial Fibrillation	10.8%	10.2%	15.1%	0.1399
Cardiac Arrest	2.1%	2.0%	0.5%	0.3104
ICD	18.3%	15.9%	11.7%	0.076
Myectomy	4.3%	2.2%	0.5%	**< 0.01**
Unexplained Syncope	8.2%	9.2%	8.8%	0.8298
Obstruction	39.7%	40.0%	34.7%	0.4218
Genotype -1 *MYBPC3* variant -2+ *MYBPC3* variants -*MYBPC3* + other SARC gene variants	 92.4% 4.3% 3.4%	 92.7% 3.2% 4.2%	 95.1% 2.4% 2.4%	0.5225

- Younger adults (18-39 y.o. cohort) show significantly greater disease burden than older cohorts (40-59 y.o. and ≥ 60 y.o.) such as greater septal reduction therapy, need for heart transplant or left ventricular assist device, atrial fibrillation and maximum left ventricular wall thickness.

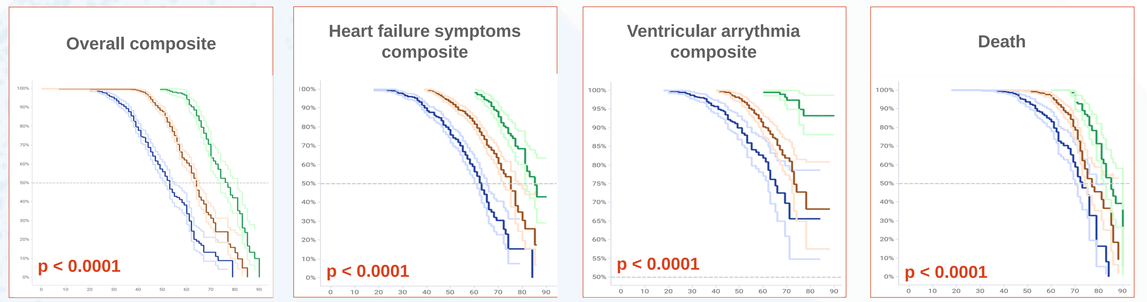
Prevalence of HCM outcomes since birth	Cohort 1: 18– 39 y.o.		Cohort 2: 40– 59 y.o.		Cohort 3: ≥60 y.o.		p-value
Overall composite[1]	262 / 656	(39.9%)	306 / 697	(43.9%)	104 / 205	(50.7%)	**0.0215**
Heart failure symptoms composite[2]	173 / 656	(26.4%)	169 / 697	(24.2%)	51 / 205	(24.9%)	0.6645
Ventricular arrhythmia composite[3]	79 / 656	(12.0%)	78 / 697	(11.2%)	13 / 205	(6.3%)	0.058
Death	71 / 656	(10.8%)	82 / 697	(11.8%)	46 / 205	(22.4%)	**0.0001**
Sudden cardiac death	18 / 71	(25.4%)	12 / 82	(14.6%)	6 / 46	(13.0%)	0.1607

Prevalence of HCM outcomes since birth	Cohort 1: 18– 39 y.o. cohort		Cohort 2: 40– 59 y.o.		Cohort 3: ≥60 y.o.		p-value
Cardiac arrest	32 / 656	(4.9%)	37 / 697	(5.3%)	2 / 205	(1.0%)	**0.0131**
Implantable cardioverter-defibrillator (ICD)	305 / 656	(46.5%)	276 / 697	(39.6%)	48 / 205	(23.4%)	**<0.0001**
ICD appropriate therapy	52 / 304	(17.1%)	52 / 271	(19.2%)	6 / 48	(12.5%)	0.5189
Atrial fibrillation	152 / 656	(23.2%)	206 / 697	(29.6%)	68 / 205	(33.2%)	**0.0039**
Cerebral vascular accident (CVA)	31 / 653	(4.7%)	56 / 697	(8.0%)	19 / 204	(9.3%)	**0.0146**
Unexplained syncope	113 / 656	(17.2%)	119 / 697	(17.1%)	30 / 205	(14.6%)	0.6969
Ventricular tachycardia/ventricular fibrillation (VT/VF)	37 / 443	(8.4%)	41 / 466	(8.8%)	10 / 136	(7.4%)	0.8935
Transplant/left ventricular assist device (LVAD)	18 / 656	(2.7%)	7 / 697	(1.0%)	0 / 205	(0%)	**0.0049**
Listed for transplant	1 / 390	(0.3%)	1 / 437	(0.2%)	0 / 125	(0%)	1
Septal reduction therapy	152 / 656	(23.2%)	123 / 697	(17.6%)	12 / 205	(5.9%)	**<0.0002**
Hospitalization associated with heart failure	33 / 443	(7.4%)	19 / 466	(4.1%)	10 / 136	(7.4%)	0.0642

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 (43.1%), heart failure symptoms composite (25.2%), ventricular arrhythmia composite (10.9%), atrial fibrillation (27.3%), and death (12.8%) across the 3 adult cohorts.
- The youngest cohort had the highest prevalence of sudden cardiac arrest, syncope, and need for transplant or left ventricular assist device.
  - Data suggests a trend towards a higher prevalence of VA composite in the youngest cohort, though this did not reach statistical significance (p = 0.058), likely due to small sample size.
- In the oldest cohort, the prevalence of overall composite outcomes, death, AF, and CVA was highest, while the incidence of cardiac arrest was the lowest.

HCM outcome – Time to Event since birth



- 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 and development of targeted therapies to restore MyBP-C levels, which could potentially modify the natural history of the disease.**

Contact information

Tenaya Therapeutics

Patient enquiries : patient.advocacy@tenayathera.com or clinical.trials@tenayathera.com