Interim results from MyCLIMB, a natural history study of pediatric *MYBPC3*-associated hypertrophic cardiomyopathy (HCM)

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Background

Mutations in *MYBPC3,* the gene that encodes cardiac myosin-binding protein C, are one of the most common genetic causes of hypertrophic cardiomyopathy (HCM). *MYBPC3*-associated childhood-onset HCM is estimated to comprise ~17% of all *MYBPC3*-driven HCM cases, with 2% of patients presenting in infancy. In the US alone, there are an estimated 3,000 pediatric patients and ~13,000 who were diagnosed before the age of 18 who are currently adults[1]

- **Pediatric-onset patients experience significantly more rapid disease progression, and a greater cumulative disease burden compared to adult-onset patients[2]**
- **Current therapeutic options include VAD, ICD, HF medications, heart transplant, etc.,[3] but are associated with considerable complication rates and do not address the underlying genetic cause of the disease**

MyCLIMB is a retrospective and prospective natural history study of 213 *MYBPC3*-associated HCM participants diagnosed before the age of 18. It was initiated in 2021 to characterize the association between genotype, structural, and functional cardiac measures over time

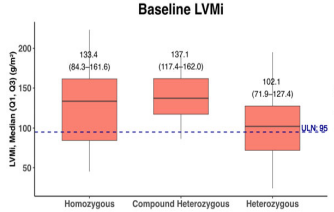
MyCLIMB Study Design and Methodology (NCT05112237)

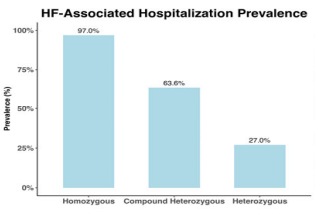
Key Eligibility Criteria for prospective cohort	➢ Diagnosis of *MYBPC3*-associated HCM ➢ MLVWT z-score ≥10 ➢ LVEF <55% or LVOT gradient ≥30 mmHg at rest
Data Collected	➢ Demographics, genotype, echocardiographic findings, and prevalence and timing of major cardiac events ➢ 27 centers across the USA, Canada, Spain, and the UK[4]
Methods	➢ Baseline data were summarized using descriptive statistics. Survival analysis was performed using Kaplan-Meier estimation. ➢ Patients were stratified based on genetic inheritance: Homozygous (with two P/LP truncating variants in *MYBPC3*), Compound Heterozygous (with one P/LP truncating variant and one missense variant in *MYBPC3*), Heterozygous (with one P/LP variant in *MYBPC3)* ➢ Among heterozygous phenotype positive patients, we identified a cohort who had a confirmed diagnosis of HCM, and longitudinal echocardiographic data collected prior to any event contained within a composite outcome. We evaluated the association echocardiographic features with outcome using Cox proportional hazards model, controlling for age of diagnosis and gender. ➢ 54 genotype positive and phenotype negative heterozygous individuals, 2 homozygous and 2 compound heterozygous patients without CM diagnosis were excluded from the analysis

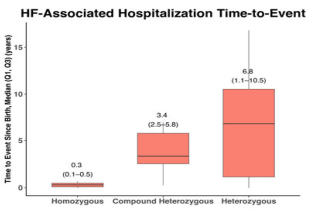
Results: Classified by Genetic Inheritance (all data as of July 2025)

- 173 retrospective and 42 prospective subjects have been enrolled in MyCLIMB (2 subject enrolled in both cohorts)
- 64% were males and **93% of patients did not have LVOT obstruction** (i.e., classified as non-obstructive phenotype)
- **LVMI was found to be a significant predictor of risk (HR = 1.01, p=0.045), with every 10-unit (g/m2) increase associated with an 10% higher hazard of a serious event**

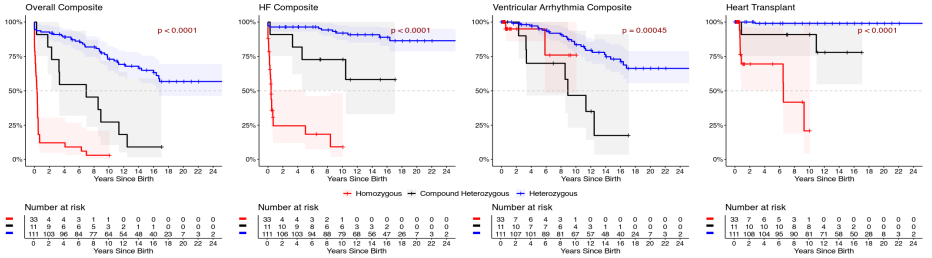
MYBPC3 Homozygous (N = 33)	*MYBPC3* Compound Heterozygous (N = 11)	*MYBPC3* Heterozygous (N = 111)
➢ Med. age of diagnosis was 0.2 years ➢ Med. LVMI was 133.4 and Z-score 11.9 ➢ Med. LVWT Index was 21.2 ➢ Med. LVEF% was 32.4 ➢ LV fractional shortening was 20.7 ➢ 85% experienced death or heart transplant	➢ Med. age of diagnosis was 2.9 years ➢ Med. LVMI was 137.1 and Z-score 10.5 ➢ 63.6% experienced a heart-failure related hospitalization during the 3.35 median years follow up ➢ 27% experienced death or heart transplant	➢ Med. age of 6.5 years at diagnosis ➢ Med. LVMI was 102.1 at diagnosis and Z-score 5.8 ➢ 27% experienced heart-failure related hospitalizations and 12.6% experienced arrhythmia-related symptoms ➢ 2.7% experienced death/heart transplant







Results: Interim Outcomes from Time of Birth



FOOTNOTE: (1) Overall Composite: HF Composite, OR Ventricular Arrhythmia Composite, OR CV-related hospitalization, OR septal reduction therapy, OR Death, OR Transplant (LVAD or heart); (2) Heart Failure Composite: LV systolic dysfunction with LVEF <50%, Mech Vent support, Mech Circ support, Parenteral Inotropic Support; (3) VA Composite: Significant arrhythmia (including VA, VT, AF), OR ICD placement, OR Pacemaker, OR Aborted SCD, OR Syncope; (4) Heart Transplant

Conclusions

- **MyClimb data demonstrates that children with *MYBPC3*-associated cardiomyopathy are at risk for severe morbidity and life-altering outcomes, even in childhood**
  - Being homozygous is devastating; nearly all children either die or require transplant before 1 year of age[5]
  - Compound heterozygous patients experienced severe cardiomyopathy with significant arrythmia burden and high prevalence of heart-failure related hospitalization, transplant or death
  - Heterozygous children with more pronounced hypertrophy experience significant burden of disease including arrhythmia and hospitalization due to heart failure
- **Genetic diagnosis, genetic counselling, and close monitoring for children with HCM is critical**
- **Current treatment options are limited for children with *MYBPC3*-associated HCM**
  - Since non-obstructive HCM is the predominant form in children, therapies primarily targeting obstructive phenotypes and not addressing the underlying genetic cause may be less effective in this severe pediatric population

NOVEL FINDING:

- **Initial modelling suggests LVMI is a strong, independent risk factor for poor long-term outcomes in compound heterozygous and heterozygous groups**
  - LVMI may therefore be an appropriate surrogate marker to evaluate the early effectiveness of gene therapy (as has been accepted by regulatory agencies for other forms of genetic cardiomyopathy[7])

References

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Contact Information and Disclosures

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