**Comparing Clinical Course of Hypertrophic Cardiomyopathy in Sarcomere Variant Carriers and Non-Carriers**

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**Running Title:** Sarcomeric and non-sarcomeric HCM

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**ABSTRACT:**

***Background***: Rare variants in sarcomere genes is a common cause of hypertrophic cardiomyopathy (HCM). However, genetic testing is negative for a monogenic cause, in a significant proportion of patients. Previous research suggests phenotypic differences to exist between patients with and without sarcomere variants, but a comprehensive comparison of their clinical courses remains unexplored.

***Methods***: We conducted a longitudinal cohort study including patients with HCM from 12 international, high-volume cardiomyopathy clinics. Inclusion required genetic testing that had either identified pathogenic or likely pathogenic variants (LP/P) in the 8 classic sarcomere genes, or gene-elusive HCM. Clinical characteristics and prognosis were compared between these groups.

***Results***: We included 5,454 patients (38% female, 89% probands, 50% carriers of LP/P variants). Patients with sarcomeric HCM were younger at diagnosis (median age 36.7 vs 49.6 years), and had a lower burden of cardiovascular co-morbidities (e.g., obesity, hypertension, etc.). Comparing markers of cardiac function and remodeling revealed higher LV ejection fraction (+1.6 %-points [CI: 1.0-2.1]) and LV gradient (+19.7 mmHg [CI: 17.4-22.0]) in non-sarcomeric HCM, and larger LV wall thickness in sarcomeric HCM (+1.3 mm [CI: 0.9 to 1.6]). Incidence of LV obstruction was twice as high in non-sarcomeric HCM, but was not associated with a poorer prognosis. Conversely, the risk of atrial fibrillation, LV systolic dysfunction and ventricular arrhythmias were higher in sarcomeric HCM, with age-adjusted incidence rates approximately 33% higher than in non-sarcomeric HCM. While all-cause mortality was similar in both groups (around 10%), patients with sarcomeric HCM were younger at death, and had twice as high an incidence of HCM-related death (dying from sudden cardiac death, heart failure or stroke.

***Conclusions***: Sarcomeric and non-sarcomeric HCM present distinct clinical characteristics, cardiac phenotypes, and outcomes. Sarcomeric HCM is associated with a younger age at diagnosis, higher incidence of arrhythmias, and adverse cardiovascular events leading to higher mortality rates. These differences in cardiac phenotype may have important clinical implications for future risk stratification and treatment selection.

***Keywords:*** hypertrophic cardiomyopathy, Cardiovascular outcomes, heart failure, genetics

**CLINICAL PERSPECTIVE**

**What is new?**

* Hypertension, obesity and left ventricular obstruction were more common in gene-elusive HCM, but was not associated with a higher rate of end-stage heart failure outcomes or sudden cardiac death.
* Patients with sarcomeric HCM had a higher risk of cardiac arrhythmias and LV systolic dysfunction and an HCM-related mortality rate twice that of patients with non-sarcomeric HCM.
* Atrial fibrillation and LV systolic dysfunction were important precursors of ventricular arrhythmias and end-stage heart failure outcomes in both sarcomeric and non-sarcomeric HCM.

**What are the clinical implications?**

* Tailored management strategies targeting hypertension control and risk factor modification may benefit non-sarcomeric HCM patients.
* Sarcomeric HCM patients may require more intensive screening and surveillance for cardiac arrhythmias and LV dysfunction.
* Genetic testing information could potentially improve clinical risk stratification algorithms and predictive models for cardiovascular outcomes.

**Abbreviations**

BMI = Body-mass index

HCM = Hypertrophic cardiomyopathy

ICD = implantable cardioverter defibrillator

LV = Left ventricle

NYHA = New York Heart Association

P/LP = Pathogenic or likely pathogenic

SHaRe = Sarcomeric Human Cardiomyopathy Registry

VT = ventricular tachycardia

**INTRODUCTION**

Hypertrophic cardiomyopathy (HCM) is a complex cardiovascular disorder characterized by left ventricular hypertrophy. HCM is the most common inherited cardiomyopathy, with an estimated prevalence of 1 in 500 individuals in the general population. 1 Although HCM can arise from different etiologies, a significant proportion of cases are attributed to variants in genes encoding sarcomere proteins, such as *MYH7*, *MYBPC3*, *TNNT2*, and others. 2,3 These genetic variants are associated with familial HCM, although a pronounced variation in clinical presentation and outcomes is seen between individual variant carriers, 4 likely influenced by a range of modifiable and non-modifiable factors. 5–8 Previous studies have investigated the impact of specific genetic mutations on HCM phenotypes, prognosis, and management. 9,10 However, a comprehensive comparison of the clinical course in patients with sarcomere variants to those with non-sarcomeric HCM is still limited. Understanding the differences in disease progression, the influence of risk factors, and outcomes between these two groups is crucial for optimizing patient care and informing personalized treatment strategies. In light of these gaps in the current literature, our study aims to compare the prognosis and outcomes of patients with sarcomeric and non-sarcomeric HCM, with a particular focus on the clinical trajectories of these two sub-groups of patients. By analyzing this in a large cohort of HCM patients, we seek to uncover potential patterns that may provide valuable insights into disease progression, risk stratification, and therapeutic interventions in both sarcomeric and non-sarcomeric HCM populations.

**METHODS:**

***Study Design:***

This was a multicenter observational study using data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe).SHaRe is a longitudinal database of patients with HCM who have undergone clinical evaluation at 12 international, high-volume, expert HCM centers.

Collected data include cardiovascular events prior to SHaRe entry, demographics, clinical characteristics, echocardiographic measurements, genetic testing results, cardiovascular comorbidities, and longitudinal, prospective assessment of outcomes as previously described.9 Institutional review board and ethics approval was obtained in accordance with local policies at each SHaRe site.

***Population:***

This study included patients who had undergone clinical evaluation and genetic testing for sarcomere gene variants at a SHaRe site. Patients were stratified into two groups based on the presence or absence of pathogenic or likely pathogenic (P/LP) variants in 8 sarcomere genes (*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3*, and *ACTC*).12 Patients carrying variants of uncertain significance (or with no genetic testing) were excluded. Genetic variants were classified based on criteria of the American College of Medical Genetics and Genomics and Association for Molecular Pathology.11,12 Patients carrying LP/P sarcomere variants were defined to have sarcomeric HCM, while patients negative for sarcomere variants were defined to have non-sarcomeric HCM.

***Clinical Features:***

In this study, we aimed to compare the clinical features between patients with sarcomeric and non-sarcomeric HCM. Features of interest were selected based on their clinical relevance and potential impact on patients' morbidity and mortality. These features were categorized into the following groups:

1. Cardiovascular comorbidities: Hypertension and obesity (BMI > 30).
2. Cardiac re-modeling and function: left ventricular (LV) ejection fraction, LV outflow gradient, max LV wall thickness, and left atrial size.
3. Heart failure outcomes: New York Heart Association (NYHA) functional class III-IV symptoms, LV systolic dysfunction, and cardiac transplantation or LV assist device implantation.
4. Arrhythmic features: Syncope, non-sustained ventricular tachycardia (VT), cardiac arrest, composite ventricular arrhythmia outcome (including sudden cardiac death, aborted sudden cardiac death, sustained ventricular tachycardia and appropriate implantable cardioverter-defibrillator [ICD] therapy), and atrial fibrillation.
5. Interventional outcomes: ICD implantation, septal reduction therapy (surgical myectomy or alcohol septal ablation), arrhythmia ablation.
6. Cerebrovascular outcome: Stroke.
7. Mortality: All-cause and cause-specific mortality including HCM-related mortality. HCM-related mortality included sudden cardiac death, heart failure and stroke as causes of death.

These phenotypic features were assessed and compared between the sarcomeric and non-sarcomeric HCM groups to determine the differences in their clinical courses and overall prognosis. The occurrence, timing, and sequence of these outcomes were analyzed to better understand the natural history of HCM and the potential influence of genetic etiology on disease progression and management.

***Statistical Analyses*:**

SHaRedata through June 2022 were analyzed. Continuous variables were presented as mean ± SD if normally distributed or as median (interquartile range, IQR) if deviating substantially from the normal distribution as evaluated by quantile-quantile plots. Categorical variables are presented as counts and percentages. Between group comparisons were evaluated statistically using Welch’s t-test, Wilcoxon rank sum test, Fisher’s exact test or Chi-square tests as appropriate.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for comparing the clinical characteristics of patients with sarcomeric and non-sarcomeric HCM. For the analysis of cardiac function and remodeling, we report results from both simple linear regression and multivariable linear regression to adjust for age, sex, and body surface area.

We computed the relative risk of cardiovascular comorbidities and adverse events in patients with non-sarcomeric and sarcomeric HCM. The incidence of cardiovascular outcomes during follow-up was compared using the Kaplan-Meier method and log-rank tests. In addition, age-specific incidence rates were reported according to five age groups (<30, 31-45, 46-55, 56-65 and >65 years of age), corresponding to the distribution of age in quintiles of the SHaRe cohort. Age-standardized incidence rates were calculated, and Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI, adjusting for potential confounders. Age-specific and -standardized rates were compared by computing a standardized incidence ratio and the reference age was set to be the age-distribution of the combined cohort at the time of study inclusion.

To assess the clinical course of HCM over time, we evaluated the sequence and timing of LV obstruction, atrial fibrillation, onset of NYHA class III-IV symptoms, LV systolic dysfunction, a composite ventricular arrhythmia outcome, stroke, cardiac transplantation or LV assist device implantation, and death. Cox proportional hazards modeling using age as the time-scale, left-truncated at time of first SHaRe visit, and including obesity, hypertension, LV obstruction, atrial fibrillation, LV systolic dysfunction and the composite ventricular arrhythmia outcome as time-varying co-variates was performed to evaluate the temporal co-occurrence of each cardiovascular feature to examine if these features were exposures associated with down-stream cardiovascular outcomes. Patients with sarcomeric and non-sarcomeric HCM were evaluated in separate models and reported hazard ratios are adjusted hazard ratios, corrected (Bonferroni) for multiple testing. Finally causes of death were compared between patients with sarcomeric and non-sarcomeric HCM.

A p-value of <0.05 was considered significant. Statistical analyses were conducted using R version 4.1.1 (R Foundation for statistical computing, Vienna, Austria), and the packages *tidyverse*, *broom*, *ggtext*, *scico*, *survival*, *survMiner*, *epiR*, *epitools*, *gt*, *gtsummary*, *patchwork* and *janitor*. Due to the sensitive nature of the data collected for this study, the data that support the findings of this study are not publicly available. The code for statistical analysis and creating figures can be found online13.

**RESULTS:**

**Clinical Characteristics of Patients:**

This study focused on 5,454 patients (38% female, 89% probands) diagnosed with HCM in whom genetic testing had been performed and either identified a LP/P genetic sarcomere variant (n= 2715) or been negative (n= 2739). Median age at time of HCM diagnosis was 46.1 years (IQR: 30.4 to 58.3), while the age at inclusion in SHaRe was 50 years (IQR: 35 to 62). At the first clinical visit at a SHaRe site, hypertension was prevalent or had been diagnosed in 29%, atrial fibrillation in 13%, stroke in 2.8% while 10% had a history of syncope and 2.1% a history of cardiac arrest.

**Clinical characteristics in Sarcomeric vs Non-sarcomeric HCM**

Clinical characteristics according to genetic subgroup are presented in **Table 1**. Notably, the median age at HCM diagnosis was markedly lower in sarcomeric vs non-sarcomeric HCM (median age 36.7 vs 49.6 years). Patients with non-sarcomeric HCM were less likely to be female (OR 0.71 [CI, 0.64-0.80]), white (OR 0.71 [CI, 0.64-0.80]), or report a family history of sudden cardiac death (OR 0.36 [CI, 0.30-0.42]), but more likely to be obese (BMI>30, OR 1.73 [CI, 1.52 to 1.97]), have hypertension (OR 2.62, [CI, 2.29 to 3.01]), LV obstruction (gradient >30mmHg, OR 1.94 [CI, 1.68 to 2.25]), and report significant dyspnea at baseline (New York Heart Association [NYHA] functional class III-IV).

**Cardiac Function and Remodeling in Sarcomeric vs Non-sarcomeric HCM**

Measures of cardiac function and remodeling were relatively similar between the two groups. However, patients with non-sarcomeric HCM had higher LV ejection fraction (+1.6 %-points [CI: 1.0 to 2.1], p <0.001), and a markedly higher LV gradient (+19.7 mmHg [CI: 17.4 to 22.0], p <0.001), with both measures remaining significant after correction for age and sex (+2.2 %-points [CI: 1.6 to 2.8], p <0.001 for LVEF and 17.2 mmHg [CI: 14.7 to 19.7], p <0.001 for LV gradient). In contrast, patients with sarcomeric HCM had larger max LV wall thickness, both in absolute terms (+1.3 mm [CI: 0.9 to 1.6], p <0.001) and when converted to z-scores (+1.5 z [CI: 1.1 to 1.9], p <0.001). Finally, we investigated the peak oxygen uptake from 2895 cardiopulmonary exercise tests, performed in 1537 patients (50% with sarcomeric HCM), and found that carrying a sarcomere variant was associated with a lower peak oxygen uptake (-2.2 ml O2/kg/min [CI: -2.8 to -1.6], p <0.001), when adjusted for age, sex, BMI, presence of atrial fibrillation and effort (-0.6 [CI: -1.3 to 0.1], p = 0.083, in unadjusted analysis).

**Comparison of non-sarcomeric and sarcomeric HCM phenotype**

To compare the phenotypes of non-sarcomeric and sarcomeric HCM, we computed the relative risk of cardiovascular co-morbidities and adverse events in patients with non-sarcomeric and sarcomeric HCM. Results from this comparison is presented in **Figure 1**. Overall, patients with non-sarcomeric HCM were more likely to have classic cardiovascular co-morbidities (RR for hypertension RR 1.83 [CI 1.72-1.97]; RR for obesity RR 1.46 [CI 1.34-1.60]) and an obstructive phenotype (RR 1.51 [CI 1.42-1.60]), and patients with sarcomeric disease were more likely to be diagnosed with cardiac arrhythmias (RR for atrial fibrillation 1.12 [CI 1.02-1.22] and RR for composite VT 1.92 [CI 1.60-2.31]) and left ventricular systolic dysfunction (RR 1.72 [CI 1.45-2.04]). Based on this, we compared the incidence of LV obstruction, cardiac arrhythmias and LV systolic dysfunction during follow-up (excluding patients in whom these outcomes were prevalent at baseline).

**LV obstruction**

The incidence of LV obstruction was evaluated during a total of 17.154 person-years of follow-up in 2456 patients, not diagnosed with LV obstruction at baseline and with information from at least one follow-up echocardiography. The cumulative incidence of LV obstruction was markedly higher in patients with non-sarcomeric HCM during follow-up, with a cumulative incidence of 28% (CI: 25-31) vs 15% (CI: 13-17) at 5 years of follow-up (**Supplementary Figure 1a**). Next, we evaluated the age-specific incidence of LV obstruction in five age-groups and found the incidence to be higher in patients with non-sarcomeric HCM in all evaluated age-groups (**Supplementary Figure 1b**), with an age-standardized incidence rate of LV obstruction of 54 (CI: 48-61) vs 26 (CI: 24-30) per 1.000 person-years in sarcomeric HCM. Since patients with non-sarcomeric HCM also had a higher burden of cardiovascular risk factors, we evaluated the time to LV obstruction from first echocardiography in SHaRe, adjusted for age at HCM diagnosis, sex, presence of hypertension or obesity and being a proband, and found having non-sarcomeric HCM to be associated with an adjusted HR of 1.59 (CI: 1.32-1.92).

**Cardiac arrhythmias**

The incidence of atrial fibrillation was evaluated during a total of 29.923 person-years of follow-up in 4.270 patients, not diagnosed with atrial fibrillation at baseline. The cumulative incidence of atrial fibrillation was similar in non-sarcomeric and sarcomeric HCM during follow-up (log-rank p =0.078) (**Figure 2a**). However, the age-specific incidence of atrial fibrillation was numerically higher in patients with sarcomeric HCM, across all evaluated age-groups (**Figure 2c**) with an age-standardized incidence rate of atrial fibrillation of 27 (CI 24-30) vs 21 (CI: 19-24) per 1.000 person-years, corresponding to a standardized incidence ratio of 1.34 (CI: 1.21 to 1.47, p <0.0001) for atrial fibrillation in sarcomeric HCM.

The incidence of the composite ventricular arrhythmia outcome was evaluated during a total of 35.703 person-years of follow-up in 4.726 patients, without this outcome at baseline. The cumulative incidence was higher in sarcomeric HCM during follow-up (p =0.004) (**Figure 2b**). The age-specific incidence of the composite ventricular arrhythmia outcome was numerically higher in patients with sarcomeric HCM, across all evaluated age-groups (**Figure 2d**), with the most pronounced difference in patients older than 65. Overall, the age-standardized incidence rate in sarcomeric and non-sarcomeric HCM was 7.6 (CI 6.4-8.9) vs 5.4 (CI: 4.1-7.0) per 1.000 person-years, corresponding to a standardized incidence ratio of 1.35 (CI: 1.15 to 1.59, p <0.001) for this outcome in sarcomeric HCM.

**Left ventricular systolic dysfunction**

The incidence of LV systolic dysfunction was evaluated during a total of 38.410 person-years of follow-up in 4.939 patients, not diagnosed with LV systolic dysfunction at baseline. The cumulative incidence of LV systolic dysfunction was similar in during follow-up (p =0.120) (**Supplementary Figure 2a**). However, the age-specific incidence rates of LV systolic dysfunction were numerically higher in patients with sarcomeric HCM (**Supplementary Figure 2b**) with an age-standardized incidence rate of LV systolic dysfunction of 14 (CI 12-16) vs 10 (CI: 8-12) per 1.000 person-years, corresponding to a standardized incidence ratio of 1.33 (CI: 1.17 to 1.50, p <0.001) for LV systolic dysfunction in sarcomeric HCM.

**Chronological timing of cardiovascular features**

To evaluate the clinical course of HCM over time, we evaluated the time of occurrence of 6 features of interest associated with HCM (atrial fibrillation, New York Heart Association [NYHA] class III/IV symptoms, LV systolic dysfunction, a composite ventricular arrhythmia outcome, cardiac transplantation, and death). Results from this analysis can be seen in **Figure 3**, which shows the distribution of events according to age. Consistent with a younger age at diagnosis of HCM, the age-distribution of investigated features skewed younger for patients with sarcomeric HCM. In addition, we observed a sharper peak in the distribution of age at occurrence of these features in patients with non-sarcomeric HCM, mostly centered around the time of diagnosis of HCM. By comparing the kurtosis of the age distribution in non-sarcomeric vs sarcomeric HCM we found this concentration of feature occurrence in patients with non-sarcomeric HCM to be most apparent for the age at death (excess kurtosis of 3.32 vs 1.34), NYHA III/IV symptoms (excess kurtosis of 0.36 vs -0.32), ventricular arrhythmias (excess kurtosis of -0.34 vs -1.02), atrial fibrillation (excess kurtosis of 0.47 vs -0.10) and LV systolic dysfunction (excess kurtosis of 0.15 vs -0.27).

**Exploring cardiovascular exposures and connected features**

Our next objective was to evaluate the co-occurrence of cardiovascular features and assess the likelihood of their occurrence in a specific temporal pattern (i.e., one feature preceding the occurrence of another feature). To do this, we first quantified the overrepresentation of event co-occurrence by calculating the relative risks associated with being exposed to one of the other features. **Supplementary Figure 3** shows the results of this analysis. We identified 17 feature-pairs which co-occurred in a specific temporal pattern. Hypertension, obesity and obstruction, the most common features in HCM, were associated with an increased risk of NYHA class III-IV symptoms in patients with non-sarcomeric HCM, but did not significantly increase the risk of other heart failure or arrhythmic outcomes in any of the groups. The composite ventricular arrhythmia outcome was correlated with an increased risk of LV systolic dysfunction, cardiac transplantation/LVAD implantation, and death in both groups. Atrial fibrillation, was an important modifier of disease in patients with sarcomeric HCM with strong associations to heart failure outcomes and stroke, while these associations were not observed in non-sarcomeric HCM.

To further investigate the temporal association between features defined as potential exposures, with other cardiovascular outcomes, we performed multivariable Cox proportional hazards modelling, including time-varying effects of all investigated exposures. Results from this analysis can be seen in **Figure 4**. Atrial fibrillation was found to be associated with a higher rate of heart failure outcomes and stroke with stronger evidence of this association in patients with sarcomeric HCM. In addition, atrial fibrillation was associated with a higher risk of malignant ventricular arrhytmias in both groups (HR of 2.8 and 2.3). Again, LV obstruction, hypertension and obesity were not strong independent predictors of cardiac arrhytmias or heart failure outcomes.

**Mortality in sarcomeric and non-sarcomeric HCM**

Finally, we investigated the timing and causes of death in patients with sarcomeric and non-sarcomeric HCM. At the end of follow-up, 541 (9.9%) patients had died, with similar mortality in patients with sarcomeric and non-sarcomeric HCM (10% and 9.5% respectively). The mean age at time of death was lower among patients with sarcomeric HCM (63 vs 70 years, p <0.0001). Additionally, patients with sarcomeric HCM had a higher likelihood of dying from sudden cardiac death (21 vs 11% of deaths) and heart failure (27 vs 9.2% of deaths). Overall, having sarcomeric HCM was associated with an odds ratio of 2.70 (CI: 1.94 to 3.82, p<0.0001) of dying of either heart failure or sudden cardiac death. A summary of the causes of death in our cohort can be seen in **Supplementary Table 1**. Next, we sought to investigate the cumulative incidence of HCM-related death, from time of inclusion in SHaRe and the age-specific incidence of HCM-related death in patients with sarcomeric and non-sarcomeric HCM. Results from this analysis can be seen in **Figure 6**, which shows a higher cumulative incidence of HCM-related death during follow-up (corresponding to a hazard ratio of 1.69 [CI: 1.22 to 2.35, p =0.002] in Cox modelling), and a significantly higher age-specific incidence in patients older than 45 years of age, with an overall standardized incidence ratio of 2.3 (CI: 1.9 to 2.7) for HCM-related death in patients with sarcomeric HCM. Patients with LP/P sarcomere variants were also found to have a higher age-standardized incidence of cardiovascular death (SIR 1.90 [CI: 1.61 to 2.23) and all-cause mortality (SIR 1.27 [CI: 1.13 to 1.43]) (**Supplementary Figure 4**)

**DISCUSSION:**

Our study presents a comprehensive comparison of the clinical course of sarcomeric and non-sarcomeric HCM in a large observational cohort. We discovered that these two causes of HCM correlate with distinct cardiac phenotypes. Notably, patients with sarcomeric HCM were diagnosed younger, had a higher burden of cardiac arrhythmias, more severe heart failure and had an HCM-related mortality-rate twice that of their non-sarcomeric counterparts. In contrast, non-sarcomeric HCM patients were more likely to be obese, have hypertension, report substantial dyspnea and be diagnosed with LV obstruction. Additionally, we found atrial fibrillation and LV systolic dysfunction to be significant precursors of severe cardiovascular outcomes. Both were associated with twice as high rates of ventricular arrhythmias and end-stage heart failure outcomes in both HCM types. These findings offer valuable insights into the clinical course of these two HCM subtypes, with potential implications for risk stratification and treatment selection.

**Cardiac Function and Remodeling in Sarcomeric vs Non-sarcomeric HCM**

Comparison of the clinical characteristics and objective measures of cardiac function and remodeling associated with sarcomeric and non-sarcomeric HCM, has been characterized in prior genotype-phenotype studies. These studies have reported differences in sex, age at diagnosis, presence of co-morbidities, LV wall thickness and LV gradient, consistent with those reported here. 9,14–16 However, previous studies have not identified a difference in LVEF or in cardiovascular fitness between sarcomeric and non-sarcomeric HCM patients. It should be noted that the mean LVEF was >65% in both groups, in line with our current understanding of HCM as a hypercontractile disease.17,18 Even then, the finding of a lower LVEF in sarcomere variant carriers, could be an indicator of the increased risk of incident LV systolic dysfunction in sarcomeric HCM, which has been reported in both childhood- and adult-onset HCM. 19,20 In general, patients with HCM have a moderate reduction in exercise capacity. Although the difference in maximum oxygen uptake was insignificant in unadjusted analysis, when adjusting for factors known to correlate with peak oxygen uptake, 21,22 patients with sarcomeric HCM had a 10% lower exercise capacity compared to patients with non-sarcomeric HCM. This finding highlights the importance of encouraging regular exercise training, specifically for individuals with sarcomeric HCM, to improve their functional capacity and quality of life. 23–28

**Cardiovascular Outcome Features More Specific to Non-sarcomeric HCM**

Our study expands on previous studies which have highlighted the heterogeneity of HCM phenotypes based on the underlying genetic substrates of HCM. Consistent with prior studies, we observed that patients with non-sarcomeric HCM were more likely to have classic cardiovascular comorbidities and an obstructive phenotype.9,14,15,29 However, we add to this knowledge, by providing detailed information on the timing and downstream effect of LV obstruction. Remarkably, we found that the age-specific incidence of LV obstruction in non-sarcomeric HCM to be at least 40% higher than in sarcomeric HCM across all examined age-groups. Overall, the age-standardized incidence rate was twice as high in non-sarcomeric HCM. We also investigated potential features predisposing patients to onset of LV obstruction and identified obesity to be an independent risk factor, associated with a HR of 1.58 and 1.32 for developing LV obstruction in sarcomeric and non-sarcomeric HCM respectively. This is consistent with the proposed impact of obesity reported previously.30 Nevertheless, while LV obstruction has previously been associated with an higher risk of ventricular arrhythmias, stroke and death, 31 our study did not find LV obstruction to be linked to these outcome. However, we did find a strong association between LV obstruction and emergence of NYHA class III/IV symptoms irrespective of HCM etiology. In patients with sarcomeric HCM, we also found LV obstruction to associate with onset of atrial fibrillation.

Hypertension and specifically an inappropriate response to elevated diastolic blood pressure is considered to be an important exposure leading to HCM in patients with non-sarcomeric disease. 7,32 In accordance with this, the prevalence of hypertension was almost twice as high in non-sarcomeric HCM, and was diagnosed in more than half of these patients. However, the impact of hypertension on progression of HCM has sparsely been investigated previously. In this study, we found that hypertension did not associate with other adverse cardiovascular outcomes in time-to-event analysis in either non-sarcomeric or sarcomeric HCM.

**Cardiovascular Outcome Features More Specific to Sarcomeric HCM**

In contrast, patients with sarcomeric HCM were found to have a higher prevalence of all cardiac arrhythmias and LV systolic dysfunction. Even though the cumulative incidence of LV systolic dysfunction and atrial fibrillation were similar when monitored from the first visit at a SHaRe site, the age-specific incidence was consistently higher across all age-groups. Overall, the age-standardized incidence rate was approximately 33% higher in patients with sarcomeric HCM for both outcomes. Notably, both atrial fibrillation and LV systolic dysfunction were important precursors of adverse cardiovascular outcomes, with a stronger association in patients with sarcomeric HCM. This suggests that healthcare providers should pay particular attention to these outcomes, especially in patients with sarcomeric HCM, both since they are amenable to medical intervention but also since they suggest a poorer long-term prognosis.

The cumulative incidence of the composite ventricular arrhythmia outcome was higher in sarcomeric HCM during follow-up. Investigation of age-specific incidence rates revealed that the largest relative difference in incidence was observed in patients older than 65.

Finally, we report patients with sarcomeric HCM to have an HCM-related mortality rate double that of non-sarcomeric HCM. Closer analysis of mortality patterns according to age, revealed that the age-specific HCM-related mortality diverges in the two groups from age 45 onwards. The largest relative difference in HCM-related mortality in patients between the age of 46 and 55, where the rate is 3.7 times higher in patients with sarcomeric HCM.

**Future Directions and Clinical Implications**

The findings from this study have important implications for clinical practice, therapeutic management and future research in HCM. Non-sarcomeric HCM was characterized by a higher burden of cardiovascular risk factors and LV obstruction, and these patients may benefit from tailored management strategies targeting hypertension control and risk factor modification. On the other hand, patients with sarcomeric HCM were more likely to die of HCM-related causes, progress to LV systolic dysfunction and experience cardiac arrhythmias.

Patients with sarcomeric HCM, may require more intensive screening for and surveillance of cardiac arrhythmias and LV dysfunction. Not least since these outcomes are associated with a relatively bad prognosis.19,20,22 Current risk stratification algorithms used to assess risk of sudden cardiac death in HCM, to guide implementation of ICDs does not include information from genetic testing 33–35. However, in this study carrying a LP/P genetic variant in a sarcomere gene was associated with a standardized incidence ratio of 1.35 for a composite ventricular arrhythmia outcome, and notably with the highest relative and absolute difference in elderly patients (>65 years). This suggests that implementing this information into future models could improve model performance. Furthermore, LV systolic dysfunction was also identified to be a risk factor for ventricular arrhythmias with a HR> 2 in both sarcomeric and non-sarcomeric HCM, suggesting that information on systolic functioning could potentially be another relevant feature to include, in a risk prediction model for SCD. Looking forward, future research should aim to further investigate the underlying mechanisms contributing to the observed differences in disease progression and outcomes between patients with sarcomeric and non-sarcomeric HCM. Moreover, advancements in genetic profiling techniques and comprehensive phenotyping approaches may provide further insights into the complex interplay between genetic variants, clinical characteristics, and disease progression in HCM.

**Limitations**

Several limitations should be acknowledged in this study. First, our sample was limited to patients followed at high-volume referral centers, and our cohort primarily consists of probands and individuals with Caucasian ancestry, and does not fully represent the general population of patients with HCM. Second, the study had a pragmatic, real-world, partially retrospective observational design, and therefore, is subject to a potential selection and information bias. Third, although we attempted to control for potential confounders through various adjustments, there may be residual confounding that could impact the results of the study. Finally, we did not have comprehensive data on the use of guideline-directed medical therapy and the potential impact of drugs on cardiovascular co-morbidities or occurrence of outcomes could not be evaluated.

**Conclusion**

In conclusion, our study provides insights into the clinical course of cardiovascular features in patients with sarcomeric and non-sarcomeric HCM and contributes to our understanding of the heterogeneity within HCM. We identified distinct differences in clinical characteristics, temporal progression, and outcomes which underscore the importance of genetic characterization in guiding risk stratification, surveillance, and management strategies. Continued research in this field will further refine our understanding of HCM pathophysiology and pave the way for personalized approaches to patient care.

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**CONFLICT OF INTEREST AND DISCLOSURES:**

CRV, JCS, TDR and CSEM declare no relevant disclosures or competing interests.

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**References**

1. McGurk KA, Zhang X, Theotokis P, Thomson K, Harper A, Buchan RJ, Mazaika E, Ormondroyd E, Wright WT, Macaya D, et al. The penetrance of rare variants in cardiomyopathy-associated genes: a cross-sectional approach to estimate penetrance for secondary findings [Internet]. 2023 [cited 2023 Mar 29];2023.03.15.23287112. Available from: https://www.medrxiv.org/content/10.1101/2023.03.15.23287112v1

2. Ho CY, Charron P, Richard P, Girolami F, Van Spaendonck-Zwarts KY, Pinto Y. Genetic advances in sarcomeric cardiomyopathies: state of the art. *Cardiovasc. Res.* 2015;105:397–408.

3. Biddinger KJ, Jurgens SJ, Maamari D, Gaziano L, Choi SH, Morrill VN, Halford JL, Khera AV, Lubitz SA, Ellinor PT, et al. Rare and Common Genetic Variation Underlying the Risk of Hypertrophic Cardiomyopathy in a National Biobank. *JAMA Cardiol.* 2022;7:715–722.

4. Repetti GG, Kim Y, Pereira AC, Ingles J, Russell MW, Lakdawala NK, Ho CY, Day S, Semsarian C, McDonough B, et al. Discordant clinical features of identical hypertrophic cardiomyopathy twins. *Proc. Natl. Acad. Sci. U. S. A.* 2021;118:e2021717118.

5. Butters A, Lakdawala NK, Ingles J. Sex Differences in Hypertrophic Cardiomyopathy: Interaction With Genetics and Environment. *Curr. Heart Fail. Rep.* 2021;18:264–273.

6. Eberly LA, Day SM, Ashley EA, Jacoby DL, Jefferies JL, Colan SD, Rossano JW, Semsarian C, Pereira AC, Olivotto I, et al. Association of Race With Disease Expression and Clinical Outcomes Among Patients With Hypertrophic Cardiomyopathy. *JAMA Cardiol.* 2020;5:83–91.

7. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, Waring A, Ormondroyd E, Kramer CM, Ho CY, et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. *Nat. Genet.* 2021;53:135–142.

8. Lopes LR, Losi M-A, Sheikh N, Laroche C, Charron P, Gimeno J, Kaski JP, Maggioni AP, Tavazzi L, Arbustini E, et al. Association between common cardiovascular risk factors and clinical phenotype in patients with hypertrophic cardiomyopathy from the European Society of Cardiology (ESC) EurObservational Research Programme (EORP) Cardiomyopathy/Myocarditis registry. *Eur. Heart J. Qual. Care Clin. Outcomes*. 2022;9:42–53.

9. Ho Carolyn Y., Day Sharlene M., Ashley Euan A., Michels Michelle, Pereira Alexandre C., Jacoby Daniel, Cirino Allison L., Fox Jonathan C., Lakdawala Neal K., Ware James S., et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy. *Circulation*. 2018;138:1387–1398.

10. Helms Adam S., Thompson Andrea D., Glazier Amelia A., Hafeez Neha, Kabani Samat, Rodriguez Juliani, Yob Jaime M., Woolcock Helen, Mazzarotto Francesco, Lakdawala Neal K., et al. Spatial and Functional Distribution of MYBPC3 Pathogenic Variants and Clinical Outcomes in Patients with Hypertrophic Cardiomyopathy. *Circ. Genomic Precis. Med.* [Internet]. [cited 2020 Sep 9];0. Available from: https://www.ahajournals.org/doi/10.1161/CIRCGEN.120.002929

11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 2015;17:405–423.

12. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 2018;20:899–909.

13. Vissing CR. Comparing Clinical Course of Hypertrophic Cardiomyopathy in Sarcomere Variant Carriers and Non-Carriers [Internet]. 2023;Available from: https://github.com/christoffervi/sarc\_nonsarc

14. Lopes LR, Syrris P, Guttmann OP, O’Mahony C, Tang HC, Dalageorgou C, Jenkins S, Hubank M, Monserrat L, McKenna WJ, et al. Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart Br. Card. Soc.* 2015;101:294–301.

15. Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. *Heart Br. Card. Soc.* 2013;99:1800–1811.

16. Marston NA, Han L, Olivotto I, Day SM, Ashley EA, Michels M, Pereira AC, Ingles J, Semsarian C, Jacoby D, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. *Eur. Heart J.* 2021;42:1988–1996.

17. Nagayama T, Takimoto E, Sadayappan S, Mudd JO, Seidman JG, Robbins J, Kass DA. Control of In Vivo Contraction/Relaxation Kinetics by Myosin Binding Protein C: Protein Kinase A Phosphorylation–Dependent and –Independent Regulation. *Circulation*. 2007;116:2399–2408.

18. Lakdawala NK, Thune JJ, Colan SD, Cirino AL, Farrohi F, Rivero J, McDonough B, Sparks E, Orav EJ, Seidman JG, et al. Subtle Abnormalities in Contractile Function Are an Early Manifestation of Sarcomere Mutations in Dilated Cardiomyopathy. *Circ. Cardiovasc. Genet.* 2012;5:503–510.

19. Marstrand P, Han L, Day SM, Olivotto I, Ashley EA, Michels M, Pereira AC, Wittekind SG, Helms A, Saberi S, et al. Hypertrophic Cardiomyopathy With Left Ventricular Systolic Dysfunction: Insights From the SHaRe Registry. *Circulation*. 2020;141:1371–1383.

20. Alaiwi SA, Roston TM, Marstrand P, Claggett BL, Parikh VN, Helms AS, Ingles J, Lampert R, Lakdawala NK, Michels M, et al. Left Ventricular Systolic Dysfunction in Patients Diagnosed With Hypertrophic Cardiomyopathy During Childhood: Insights From the SHaRe Registry (Sarcomeric Human Cardiomyopathy). *Circulation*. 2023;

21. Hwang J-W, Lee S-C, Kim D, Kim J, Kim EK, Chang S-A, Park S-J, Kim SM, Choe YH, Ahn JH, et al. Determinants of Exercise Capacity in Patients With Hypertrophic Cardiomyopathy. *J. Korean Med. Sci.* 2022;37:e62.

22. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J. Am. Heart Assoc.* 2014;3:e001002.

23. Lampert R, Ackerman MJ, Marino BS, Burg M, Ainsworth B, Salberg L, Tome Esteban MT, Ho CY, Abraham R, Balaji S, et al. Vigorous Exercise in Patients With Hypertrophic Cardiomyopathy. *JAMA Cardiol.* 2023;8:595–605.

24. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, Concannon M, Dries AM, Shmargad Y, Salisbury H, et al. Effect of Moderate-Intensity Exercise Training on Peak Oxygen Consumption in Patients With Hypertrophic Cardiomyopathy: A Randomized Clinical Trial. *JAMA*. 2017;317:1349–1357.

25. Pelliccia A, Day S, Olivotto I. Leisure-time and competitive sport participation: a changing paradigm for HCM patients. *Eur. J. Prev. Cardiol.* 2023;30:488–495.

26. Dias KA, Link MS, Levine BD. Exercise Training for Patients With Hypertrophic Cardiomyopathy: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* 2018;72:1157–1165.

27. Dejgaard LA, Haland TF, Lie OH, Ribe M, Bjune T, Leren IS, Berge KE, Edvardsen T, Haugaa KH. Vigorous exercise in patients with hypertrophic cardiomyopathy. *Int. J. Cardiol.* 2018;250:157–163.

28. Klempfner R, Kamerman T, Schwammenthal E, Nahshon A, Hay I, Goldenberg I, Dov F, Arad M. Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: Results of a structured exercise training program in a cardiac rehabilitation center. *Eur. J. Prev. Cardiol.* 2015;22:13–19.

29. Curran L, Marvao A de, Inglese P, McGurk KA, Schiratti P-R, Clement A, Zheng SL, Li S, Pua CJ, Shah M, et al. A genotype-phenotype taxonomy of hypertrophic cardiomyopathy [Internet]. 2023 [cited 2023 Jun 20];2023.03.11.23285908. Available from: https://www.medrxiv.org/content/10.1101/2023.03.11.23285908v2

30. Fumagalli C, Maurizi N, Day SM, Ashley EA, Michels M, Colan SD, Jacoby D, Marchionni N, Vincent-Tompkins J, Ho CY, et al. Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy. *JAMA Cardiol.* 2020;5:65–72.

31. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of Left Ventricular Outflow Tract Obstruction on Clinical Outcome in Hypertrophic Cardiomyopathy. *N. Engl. J. Med.* 2003;348:295–303.

32. de Marvao A, Dawes TJW, Shi W, Durighel G, Rueckert D, Cook SA, O’Regan DP. Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: A High-Resolution 3D MRI Study. *JACC Cardiovasc. Imaging*. 2015;8:1260–1269.

33. O’Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur. Heart J.* 2014;35:2010–2020.

34. O’Mahony C, Akhtar MM, Anastasiou Z, Guttmann OP, Vriesendorp PA, Michels M, Magrì D, Autore C, Fernández A, Ochoa JP, et al. Effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart Br. Card. Soc.* 2019;105:623–631.

35. O’Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I, et al. An International External Validation Study of the 2014 European Society of Cardiology Guideline on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (Evidence from HCM). *Circulation*. 2017;CIRCULATIONAHA.117.030437.

**Table 1:** Clinical characteristics of the cohort at time of inclusion.

| Characteristic | SARC(+), N = 2,715 | SARC(-), N = 2,739 | p-value |
| --- | --- | --- | --- |
| **Demographic information** |  |  |  |
| Female | 1,144 (42%) | 939 (34%) | <0.001 |
| Age at HCM diagnosis | 37.5 (22.5 to 50.5) | 53.2 (41.2 to 63.0) | <0.001 |
| Age at inclusion in SHaRe | 43 (28, 55) | 56 (45, 66) | <0.001 |
| Proband | 2,154 (80%) | 2,627 (98%) | <0.001 |
| **Race** |  |  | <0.001 |
| White | 2,356 (87%) | 2,227 (81%) |  |
| Other or Not Reported | 205 (7.6%) | 280 (10%) |  |
| Black | 72 (2.7%) | 134 (4.9%) |  |
| Asian | 82 (3.0%) | 98 (3.6%) |  |
| **Objective clinical findings** |  |  |  |
| Systolic blood pressure | 120 (110 to 130) | 130 (118 to 140) | <0.001 |
| Diastolic blood pressure | 71 (65 to 80) | 76 (70 to 82) | <0.001 |
| Body mass index | 26.3 (23.1 to 30.0) | 28.1 (25.0 to 32.3) | <0.001 |
| Body surface area | 1.92 (1.73 to 2.11) | 2.00 (1.83 to 2.18) | <0.001 |
| **Echocardiography findings** |  |  |  |
| Maximal LV wall thickness | 18.0 (14.5 to 22.0) | 17.0 (14.0 to 20.0) | <0.001 |
| LV internal diameter in diastole | 43 (39 to 48) | 45 (40 to 49) | <0.001 |
| Indexed LV internal diameter in diastole | 22.7 (20.0 to 25.4) | 22.2 (19.8 to 24.9) | 0.001 |
| LV internal diameter in systole | 26 (22 to 30) | 27 (22 to 31) | <0.001 |
| Indexed LV internal diameter in systole | 13.5 (11.3 to 16.1) | 13.2 (11.2 to 15.4) | 0.003 |
| **Co-morbidities and medical history** |  |  |  |
| Hypertension | 518 (19%) | 1,054 (38%) | <0.001 |
| Atrial fibrillation | 357 (13%) | 357 (13%) | 0.9 |
| Syncope | 282 (10%) | 263 (9.6%) | 0.3 |
| Stroke | 68 (2.5%) | 85 (3.1%) | 0.2 |
| Family history of sudden cardiac death | 486 (18%) | 197 (7.2%) | <0.001 |
| History of cardiac arrest | 70 (2.6%) | 45 (1.6%) | 0.016 |
| New York Heart Association class III-IV | 196 (7.2%) | 244 (8.9%) | 0.022 |
| LV systolic dysfunction | 101 (3.7%) | 48 (1.8%) | <0.001 |
| Severe LV systolic dysfunction | 22 (0.8%) | 10 (0.4%) | 0.031 |
| **ESC risk score** |  |  | <0.001 |
| High (>6% per 5 years) | 172 (11%) | 76 (4.8%) |  |
| Moderate (4-6% per 5 years) | 215 (13%) | 122 (7.8%) |  |
| Low (<4% per 5 years) | 1,216 (76%) | 1,374 (87%) |  |
| Unknown | 1,112 | 1,167 |  |
| n (%); Median (25% to 75%) | | | |
|  | | | |

| **Table 2:** All-cause and cause-specific mortality in sarcomeric and non-sarcomeric hypertrophic cardiomyopathy | | | |
| --- | --- | --- | --- |
| **CHARACTERISTIC** | **SARC(+)**, N = 2,715 | **SARC(-)**, N = 2,739 | **P-VALUE** |
| All-cause mortality | 281 (10%) | 260 (9.5%) | 0.3 |
| Causes of death |  |  | <0.001 |
| *Non-cardiovascular death* | 93 (33%) | 147 (57%) |  |
| *Heart failure* | 77 (27%) | 24 (9.2%) |  |
| *Sudden cardiac death* | 58 (21%) | 28 (11%) |  |
| *Not Recorded* | 25 (8.9%) | 22 (8.5%) |  |
| *Other cardiovascular death* | 21 (7.5%) | 25 (9.6%) |  |
| *Malignancy* | 7 (2.5%) | 14 (5.4%) |  |

**Figure 1:**

**Legend:** Relative risk of the occurrence of 15 cardiovascular features (y-axis) in patients with sarcomeric vs non-sarcomeric hypertrophic cardiomyopathy (HCM). The relative risk ratio is given on the x-axis and the filled dots denote the point-estimate of the relative risk while the error-bars give the confidence intervals. On the right the overall prevalence of each feature is given separately for each group.

**Figure 2**

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**Legend:** Incidence of the atrial fibrillation (**A** & **C**) and composite ventricular arrhythmia (**B**, **D**) outcome in patients who are genotype-positive (pink) vs -negative (blue) for sarcomere variants. Panels **A-B.** Cumulative incidence since first SHaRe evaluation, including numbers at risk by year. Panels **C-D.** Age-specific incidence rates, including total person-years at risk in each age-group. The age-standardized incidence rate (ASI) has been added as the final group. The standardized incidence ratio (SIR) has been added for each age-group at the bottom of the plot.

**Figure 3**

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**Legend:** Histogram, showing the distribution of age (x-axis) at time of occurrence of each of six features associated with hypertrophic cardiomyopathy. Patients have been stratified into two groups according to whether they had sarcomeric (pink) or non-sarcomeric HCM (blue). The y-axis gives the raw number of patients associated with each features in a 5 year-period.

**Figure 4:**



**Legend:** Heatmap showing the time-adjusted hazard ratios of being diagnosed with one of 8 cardiovascular features (x-axis) predicated on being exposed to one of the 7 pre-defined features (y-axis). Hazard ratios larger than 1 are shown with Bonferroni corrected 95% confidence intervals if Bonferroni corrected p <0.05 (i.e. uncorrected p <0.007).

**Figure 5**

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**Legend:** Incidence of hypertrophic cardiomyopathy (HCM) related mortality in patients who are genotype-positive (pink) vs -negative (blue) for sarcomere variants. Panel **A.** Cumulative incidence since first SHaRe evaluation, including numbers at risk by year. Panel **B.** Age-specific incidence rates, including total person-years at risk in each age-group. The age-standardized incidence rate (ASI) has been added as the final group. The standardized incidence ratio (SIR) has been added for each age-group at the bottom of the plot. HCM-related mortality includes sudden cardiovascular death, heart failure related death, and death due to stroke.

**Supplementary Figure 1**



**Legend:** Incidence of obstruction in patients who are genotype-positive vs -negative for sarcomere variants. **A.** Cumulative incidence of obstruction since first SHaRe evaluation, including numbers at risk by year. **B.** Age-specific incidence rates of obstruction, including total person-years at risk in each age-group.

**Supplementary Figure 2**



**Legend:** Incidence of left ventricular systolic dysfunction in patients who are genotype-positive vs -negative for sarcomere variants. **A.** Cumulative incidence of obstruction since first SHaRe evaluation, including numbers at risk by year. **B.** Age-specific incidence rates of obstruction, including total person-years at risk in each age-group.

**Supplementary Figure 3:**



**Legend:** Heatmap showing the relative risk of occurrence of one of eight cardiovascular features (x-axis) predicated on also being diagnosed with one of seven potential exposures prior to onset of the outcomes under investigation.