



UNIVERSITÀ  
DEGLI STUDI  
FIRENZE

FLORE

## Repository istituzionale dell'Università degli Studi di Firenze

### **A Validated Model for Sudden Cardiac Death Risk Prediction in Pediatric Hypertrophic Cardiomyopathy**

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

A Validated Model for Sudden Cardiac Death Risk Prediction in Pediatric Hypertrophic Cardiomyopathy / Miron, Anastasia; Lafreniere-Roula, Myriam; Fan, Chun-Po Steve; Armstrong, Katey R; Dragulescu, Andreea; Papaz, Tanya; Manlhiot, Cedric; Kaufman, Beth; Butts, Ryan J; Gardin, Letizia; Stephenson, Elizabeth A; Howard, Taylor S; Aziz, Peter F; Balaji, Seshadri; Beauséjour Ladouceur, Virginie; Benson, Lee N; Colan, Steven D; Godown, Justin; Henderson, Heather T; Ingles, Jodie; Jeewa, Aamir; Jefferies, John L;

*Availability:*

This version is available at: 2158/1194230 since: 2020-05-21T18:33:50Z

*Published version:*

DOI: 10.1161/CIRCULATIONAHA.120.047235

*Terms of use:*

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

*Publisher copyright claim:*

(Article begins on next page)

# A Validated Model for Sudden Cardiac Death Risk Prediction in Pediatric Hypertrophic Cardiomyopathy

**Running Title:** *Miron et al.; Predicting Sudden Death in Childhood HCM*

Anastasia Miron, et al.

*The full author list is available on pages 21-22.*

**Address for Correspondence:**

Seema Mital, MD  
Hospital for Sick Children  
555 University Avenue  
Toronto, Ontario M5G 1X8, Canada  
Tel: 416-813-7418  
Fax: 416-813-5857  
Email: [seema.mital@sickkids.ca](mailto:seema.mital@sickkids.ca)



Circulation

## Abstract

**Background:** Hypertrophic cardiomyopathy (HCM) is the leading cause of sudden cardiac death (SCD) in children and young adults. Our objective was to develop and validate a SCD risk prediction model in pediatric HCM to guide SCD prevention strategies.

**Methods:** In an international multi-center observational cohort study, phenotype-positive patients with isolated HCM <18 years at diagnosis were eligible. The primary outcome variable was the time from diagnosis to a composite of SCD events at 5-year follow-up: SCD, resuscitated sudden cardiac arrest (SCA), and aborted SCD, i.e. appropriate shock following primary prevention ICD. Competing risk models with cause-specific hazard regression were used to identify and quantify clinical and genetic factors associated with SCD. The cause-specific regression model was implemented using boosting, and tuned with ten repeated four-fold cross-validations. The final model was fitted using all data with the tuned hyperparameter value that maximizes the c-statistic, and its performance was characterized using c-statistic for competing risk models. The final model was validated in an independent external cohort (SHaRe, n=285).

**Results:** Overall, 572 patients met eligibility criteria with 2855 patient-years of follow-up. The 5-year cumulative proportion of SCD events was 9.1% (14 SCD, 25 resuscitated SCA, 14 aborted SCD). Risk predictors included age at diagnosis, documented non-sustained ventricular tachycardia, unexplained syncope, septal diameter z-score, LV posterior wall diameter z-score, LA diameter z-score, peak LV outflow tract (LVOT) gradient, and presence of a pathogenic variant. Unlike adults, LVOT gradient had an inverse association, and family history of SCD had no association with SCD. Clinical and clinical/genetic models were developed to predict 5-year freedom from SCD. Both models adequately discriminated patients with and without SCD events with a c-statistic of 0.75 and 0.76 respectively and demonstrated good agreement between predicted and observed events in the primary and validation cohorts (validation c-statistic 0.71 and 0.72 respectively).

**Conclusions:** Our study provides a validated SCD risk prediction model with over 70% prediction accuracy and incorporates risk factors that are unique to pediatric HCM. An individualized risk prediction model has the potential to improve the application of clinical practice guidelines and shared decision-making for ICD insertion.

**Clinical Trial Registration:** URL: <https://clinicaltrials.gov> Unique Identifier: NCT04036799

**Key Words:** cardiomyopathy; hypertrophy; sudden cardiac death; implantable cardioverter-defibrillator; sudden cardiac arrest; pediatrics; hypertrophic cardiomyopathy

### Non-standard Abbreviations and Acronyms:

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
IVSD	interventricular septal diameter
LVPWD	left ventricular posterior wall diameter
MICE	multiple imputation by chained equations
PRIMaCY	PRecision Medicine for Cardiomyopathy
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SHaRe	Sarcomeric Human Cardiomyopathy Registry

## Clinical Perspective

### What is new?

- Pediatric hypertrophic cardiomyopathy (HCM) patients had a high 5-year cumulative sudden cardiac death (SCD) risk of 9.1%.
- A large international cohort analysis identified a positive association of unexplained syncope and non-sustained ventricular tachycardia, a non-linear association of age, septal and left ventricular (LV) posterior wall thickness and left atrial diameter, and no association of LV outflow tract gradient with SCD risk (inverse association with a gradient  $\geq 100$  mmHg).
- An integrated model that incorporated all age-appropriate risk factors provided individualized scores for 5-year SCD risk and is the first prediction model to be externally validated in an independent cohort with high performance accuracy.



### What are the clinical implications?

- The decision for primary prevention implantable cardioverter defibrillator (ICD) in pediatric HCM patients should not be based on a single risk factor but should incorporate all age-appropriate, evidence-based risk factors.
- The PRIMaCY SCD risk prediction model can be implemented within hospital electronic health systems as a point of care tool to help guide physicians in shared decision making with childhood HCM patients and families regarding primary prevention ICD.

## Introduction

Hypertrophic cardiomyopathy (HCM) is the most common form of cardiomyopathy affecting at least 1 in 500 individuals and is a leading cause of sudden cardiac death (SCD) in adolescents and young adults.<sup>1-3</sup> SCD is related primarily to the occurrence of significant arrhythmias including ventricular fibrillation (VF) or sustained ventricular tachycardia (VT).<sup>4, 5</sup> Implantable cardioverter defibrillators (ICDs) can prevent SCD by detecting and terminating sustained VT or VF. They are offered to patients who have survived documented near-death events i.e. secondary prevention ICD, or prophylactically in those who have not yet suffered an event but who are deemed at high risk for an event i.e. primary prevention ICD. Despite availability of this life-saving intervention, the lack of precision in predicting SCD risk hampers timely ICDs in at-risk individuals resulting in tragic but preventable deaths. Additionally, risk is often overestimated in lower risk patients resulting in potentially unwarranted ICD implantation.<sup>6-10</sup> This can have negative medical, psychological and financial consequences since ICD therapy is associated with a 20% complication rate, and 11% inappropriate shock rate in children (higher with epicardial ICD placement).<sup>8, 11-14</sup>

Published clinical practice guidelines define high risk for SCD by the presence of one or more clinical risk factors.<sup>4, 15, 16</sup> However, clinical practice recommendations are inconsistently and variably applied in practice likely because ICD decision-making is driven by subjective perception of risk with considerable variability in risk tolerance amongst practitioners and patients, as well as a more conservative uptake due to a higher complication rate of ICDs in pediatric compared to adult patients.<sup>8, 16, 17</sup> In recent years, the European Society of Cardiology (ESC) developed and validated a web-based tool that incorporates evidence-based clinical risk factors into an algorithm to predict 5-year sudden death risk in adult patients over 16 years old,

but does not apply to children.<sup>18-22</sup> This model did not include other potential risk factors like genetic etiology of HCM which can influence the risk of SCD.<sup>15, 23, 24</sup> In addition, studies have shown that the ESC 2014 risk prediction model had a lower sensitivity in high-risk populations. As a result, the ESC 2014 model frequently mis-identified patients who experienced a SCD event as low risk.<sup>20, 25-27</sup> A recent study from the United Kingdom (UK) reported on the performance of a SCD risk prediction model for pediatric HCM developed using 5 pre-selected clinical variables with a c-statistic of 0.69; but this model has not been externally validated.<sup>28</sup> The lack of evidence-based decision support for SCD risk prediction in childhood HCM has been identified as an important practice gap.

The purpose of our study was to develop and validate a risk prediction model for SCD in pediatric HCM using evidence-based risk factors in order to assist physicians and patients in shared decision making for primary prevention ICD implantation.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study cohort and participating centers

This was a multicenter retrospective observational cohort study of pediatric patients with clinically diagnosed childhood onset HCM. Eligibility criteria included clinical diagnosis of HCM, left ventricular (LV) posterior wall or septal thickness z-score  $\geq 2$ <sup>29, 30</sup>, age less than 18 years at the time of diagnosis, absence of a SCD event prior to diagnosis, and at least one follow-up assessment after diagnosis. Genotype-positive subjects who did not have echocardiographic evidence of LV hypertrophy and patients with known or suspected secondary causes of HCM,

i.e. clinical syndromes like RASopathies, endocrine, metabolic, mitochondrial or neuromuscular disorders, hypertension, and structural heart defects were excluded. Age at diagnosis was defined as the age at echocardiogram at which the diagnosis of HCM was made. All centers used the same echocardiographic criteria for the diagnosis of hypertrophy.

The primary cohort included patients from 11 sites participating in the PReCIson Medicine for Cardiomyopathy (PRIMaCY) study, an international registry of pediatric HCM patients launched in 2017. These included 4 Canadian, 6 United States and 1 Australian site. For model validation in an independent cohort, we used data from patients with childhood onset HCM from the Sarcomeric Human Cardiomyopathy Registry (SHaRe), a registry of 15 international centers capturing longitudinal clinical data on de-identified patients with HCM.<sup>23</sup> For the 4 sites that contributed data to both registries, any overlapping patients were excluded from the validation cohort. Clinical, genetic and outcomes data were collected from the medical records in all eligible patients from the time of diagnosis to last follow-up. Echocardiographic data was collected at initial diagnosis and at last follow-up. For patients with major cardiac events (death, transplant, SCD), data was captured prior to the event. Echocardiographic data was collected from clinical reports and where feasible, missing data was collected through a re-review of the echocardiograms at local sites by the research team. SCD events were reviewed by site investigators to confirm the cause of death. The research protocol was approved by the institutional research ethics boards at all sites and waiver of consent was obtained for this retrospective study. All patient data was de-identified for data sharing and analyses. The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

## Selection of predictor variables

To generate a risk prediction model, candidate risk factors based on the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) published clinical practice guidelines were assessed.<sup>4</sup> Echocardiographic measurements of wall thickness and chamber sizes were converted to z scores using the Boston z-score calculator.<sup>29, 30</sup> The risk factors included age at diagnosis, family history of SCD, history of recent unexplained syncope within 6 months prior to diagnosis, documented non-sustained VT (defined as  $\geq 3$  beats at  $\geq 120$  bpm on ambulatory electrocardiogram (ECG), interventricular septal diameter (IVSD) z-score, LV posterior wall diameter (LVPWD) z-score, left atrial (LA) diameter z-score, and peak resting LV outflow tract (LVOT) gradient on echocardiography. Genetic results from clinical testing were captured from medical records, and through research sequencing in a subset of patients. Data included affected gene, and variant pathogenicity i.e. pathogenic/likely pathogenic, variant of uncertain significance or benign.<sup>31</sup> Variant classification was reconfirmed using American College of Medical Genetics criteria at the core site. Patients harboring pathogenic/likely pathogenic variants in cardiomyopathy genes were considered genotype-positive (**Supplementary Table I**). Ethnicity information was only available in 102 patients and therefore was not included in the analysis.

## Statistical Analysis

All statistical analyses were performed using R v3.4.1 with survival, multiple imputation by chained equations (MICE), mboost, riskRegression and mlr packages. Clinical characteristics were summarized using descriptive statistics. Continuous variables were summarized using median and interquartile range (IQR) while categorical variables were summarized using frequencies and proportions. The primary outcome was time to an SCD event during 5-years



follow-up defined as a composite outcome of SCD, resuscitated sudden cardiac arrest (SCA) (including sustained VT/VF), and aborted SCD events i.e. appropriate shock in a patient with a primary prevention ICD. Event-free survival was estimated using the Kaplan-Meier method as was the cumulative proportion of SCD events over time.

## **Model development and performance assessment**

### *General modeling approach*

To generate a risk prediction model, the relative contribution of the clinical and genetic predictors was quantified using a competing risk model for SCD events with non-SCD death as the competing risk. This analysis was implemented using cause-specific regression. To ensure that the quantification was pertinent to the clinical context, patients were administratively censored at 5 years from first evaluation. Two models were considered – a clinical only model, and a clinical/genetic model that included genotype status of the patient. Patients harboring a pathogenic/likely pathogenic causal variant on genetic testing i.e. genotype-positive patients, were compared to patients without a causal variant on testing. We applied a model-boosting algorithm to the cause-specific hazard regression to identify and quantify the association between the candidate risk factors and the composite outcome. For continuous risk factors, the associations were modeled without the assumption of linearity using penalized *b*-splines. The estimated non-linear associations were summarized graphically. Upon the fitting of the two boosted models, we then obtained the linear predictors and baseline hazard for the SCD events. This cause-specific hazard regression implementation for competing risk data has been previously described.<sup>32</sup>

### *Model tuning*

To tune the boosting model, we applied ten repeated four-fold cross-validations to determine the

hyperparameter of the boosting model. In this exercise, we considered a small learning rate (step size) of 0.01 and a large number of steps. Within each cross-validation iteration, we imputed the missing values using MICE before training the model. This scheme of nested imputation was demonstrated in a similar prognostic study setting.<sup>33,34</sup> The plausibility of missing at random assumed in the imputation depends on the candidate risk factors. As long as the candidate risk factors considered in the study are comprehensive, as in our study, this assumption is reasonable. Next we applied the trained model and calculated the c-statistic on the cross-validation data for each step. The ‘optimal’ number of steps (i.e. the value of the boosting model hyperparameter) was the one that maximized the c-statistic averaged over all cross-validation iterations. The final model was then fitted using all data with the ‘optimal’ hyperparameter value estimated in the model tuning exercise. Given the competing risk data, separate cause-specific hazard regression models were fitted and tuned – one for SCD events and the other for non-SCD deaths. Of note, due to a small number of patients with non-SCD deaths, we only applied three-fold cross-validation to identify and quantify the risk factors associated with non-SCD deaths.

### *Model performance*

Upon model fitting, both prognostic index and the 5-year cumulative proportion of SCD events was quantified for each patient. The discriminatory power of the final model was quantified using the c-statistic for competing risk models.<sup>35</sup> Model calibration was assessed by stratifying patients into three risk groups based on tertiles of the predicted 5-year probability of a SCD event and by creating a calibration curve to show the relationship between the observed and predicted 5-year probability of events.

### *Model validation*

The final model was externally validated using an independent replication cohort consisting of

285 eligible patients from SHaRe after excluding 321 patients that overlapped with the discovery cohort. Harrell's c-statistic was calculated, and calibration curves were constructed using quantiles of predicted risk as described above.

## Results

The final derivation cohort consisted of 572 eligible phenotype-positive HCM patients diagnosed between 1987-2018. This included 535 unrelated probands and 37 affected siblings of the probands. The distribution of cases by center and by age at diagnosis is shown in **Supplemental Figure I**. Baseline clinical and echocardiographic characteristics at diagnosis for the primary and validation cohorts are displayed in **Table 1**. 368 (64%) patients had asymmetric septal hypertrophy. There were no cases of apical hypertrophy. The median age at diagnosis was 9.8 years [IQR 2.1-13.9]. The median follow-up duration was 3.9 [1.5-6.7] years (duration to either death or the last known date alive). 336 of 565 (59%) patients received beta-blockers during follow-up; medication data was not available in 7 patients. Of the 311 (54%) subjects who had genetic testing reported, 160 (28%) were identified as carrying at least one causal pathogenic/likely pathogenic variant. The affected genes in the primary and validation cohorts are shown in **Supplemental Table I**.

### Time to SCD events

Over the 2,855 total patient years of follow-up, 53 patients experienced a SCD event including 14 sudden deaths, 25 resuscitated SCA, and 14 appropriate shocks in patients with primary prevention ICDs. No patients in the cohort were phenotype-negative at the time of a SCD event. Of the 102 patients who received an ICD for primary prevention, 14 experienced an appropriate shock, 88 did not experience an appropriate shock including 23 (23%) patients with more than 5-

years follow-up after ICD, and 7 experienced an inappropriate shock. Inappropriate shock information was unavailable in 19 patients. (**Supplemental Figure II**). **Supplemental Figure III** shows the indications for primary prevention ICD implantation with 63% patients receiving an ICD for a single indication. The median time to a SCD event from diagnosis was 2.2 years [IQR 0.9-5.2], and median age at an SCD event was 14.5 years [IQR 12.4 – 17.1]. The cumulative proportion of SCD events at 1-year follow-up was 2.8% [95% CI = 1.4%, 4.2%], and at 5 years was 9.1% [6.3%, 11.9%] (**Figure 1a**).

### Clinical predictors of time to SCD events

The final clinical model included age at diagnosis, IVSD z-score, LVPWD z-score, LA diameter z-score, peak LV outflow tract gradient, non-sustained VT, and history of syncope. LA diameter z-score was imputed in 21% patients in the overall cohort, and LVOT gradient in 29% patients in the overall cohort. Of the 53 patients who experienced a SCD event, LA diameter was imputed in 13% and LVOT gradient in 17% patients. Our analysis suggested that prior history of non-sustained VT increased the likelihood of experiencing SCD events by 2.8 fold (HR [95% CI] = 2.87 [1.00, 6.57]), and prior history of syncope increased the likelihood of experiencing SCD events by 7.4 fold (HR [95% CI] = 7.40 [1.21, 32.81]) (**Table 2**). A family history of SCD was not considered an important predictor either in the overall cohort or the subset with familial HCM. **Figure 2** shows the regression-adjusted association of the continuous risk factors with the composite outcome. Each panel summarizes the non-linear association between a predictor and the SCD event. SCD risk increased with increased age at diagnosis, IVSD z-score, LVPWD z-score, and LA diameter z-score. However, this positive correlation between IVSD and LVPWD z-scores plateaued at a z-score >20. In contrast, the risk associated with peak resting LVOT gradient remained flat when the gradient was  $\leq 100$  mmHg and showed an inverse association

with SCD risk as the gradient increased further. For example, an increase in peak LV outflow tract gradient from 100 to 120 mmHg reduced the SCD risk by approximately 10%. There was no difference in the cumulative proportion of SCD events in patients with and without beta-blocker use during follow-up ( $p=0.138$ ) (data not shown). To further clarify the association with age, we compared outcomes in patients diagnosed before 5 years of age versus later (**Supplemental Table II**). A third of patients were diagnosed before 5 years of age. They had a higher frequency of non-SCD deaths and transplant compared to those diagnosed later and these non-SCD events occurred at a median age of  $<1$  year. In contrast, early onset HCM cases had an overall lower frequency of SCD events compared to those diagnosed later but the median age at SCD events was not different suggesting that the penetrance of SCD remains highest in adolescent and teenage years regardless of age at diagnosis. The overall lower frequency of SCD in early onset cases may also be related in part to the higher non-SCD mortality and transplant in early life. There were no sex-related differences in the risk for SCD events.

### **Performance of the clinical prediction model**

The final clinical model was applied to the full cohort. The c-statistic was 0.75 indicating a good discriminatory power. Subjects were stratified by tertile of predicted risk and the cumulative proportion of SCD-events over time was plotted for each tertile (**Figure 2f**). The difference in cumulative proportion of SCD-events across strata of predicted risk was significant ( $p<0.001$ ). Calibration (the agreement between the magnitude of predicted risk vs. observed risk) was assessed by stratifying predicted risk into tertiles and plotting the observed cumulative proportion of SCD-events over time against the mean predicted risk for that tertile. This showed that subjects with predicted risk in the highest tertile had the highest observed cumulative proportion of SCD-events and subjects in the lowest tertile of model-predicted risk had the

lowest observed cumulative proportion of SCD events. **Figure 2g** of the calibration curve shows good agreement between predicted and observed 5-year cumulative proportion of SCD-events for each tertile of predicted risk (**Table 3**).

### Clinical and genetic predictors of time to SCD events

The first clinical/genetic model was generated using all clinical predictors above along with genotype-positive status. Similar to the clinical model, SCD risk was higher with prior history of non-sustained VT (HR [95% CI] = 2.58 [1.00, 6.17]), and prior history of syncope (HR [95% CI] = 7.23 [1.09, 33.57]). In addition, the presence of a pathogenic/likely pathogenic variant (i.e. being genotype-positive) elevated the likelihood of experiencing SCD events (HR [95% CI] = 1.32 [1.00, 2.12]) compared to the confirmed absence of a pathogenic variant on genetic testing (**Table 2**). For continuous risk factors, **Figure 3** shows the regression-adjusted effects of the predictors on the primary outcome with a similar relationship as described in the clinical model.

### Performance of the combined clinical/genetic model

The final clinical/genetic model was applied to the full cohort to generate a cumulative proportion curve for 5-year incidence of SCD events. This showed the ability of the risk prediction model to discriminate between three tertiles of SCD risk similar to the clinical model ( $p < 0.001$ ) (**Figure 3f**). **Figure 3g** shows the calibration curve for the three risk tertiles with good agreement between predicted and observed SCD event-free survival with an overall c-statistic of 0.762 which was comparable to the clinical model (**Table 3**).

### Other models considered

Since gene involved can influence risk of SCD, we also explored the association of a pathogenic/likely pathogenic variant in *MYH7*, *MYBPC3*, or other HCM-associated genes i.e. gene-specific associations versus confirmed absence of a variant. The presence of a

pathogenic/likely pathogenic variant in *MYBPC3* was associated with a higher risk of SCD events but the increase in risk was modest i.e. HR 1.022 [1.00, 1.78]. The c-statistic of this model was 0.726, which was lower than that of the first genetic model. Therefore, this model was not considered for further validation. The study was not powered to examine the effect of variant burden on SCD risk since only 2.8% patients harbored multiple pathogenic variants.

### External validation

For independent validation of the risk prediction models, we analyzed 285 phenotype-positive childhood onset HCM patients from SHaRe. There were minor differences in clinical characteristics between the SHaRe and the primary cohorts. The SHaRe patients were older at diagnosis, and the racial distribution was 89.6% Caucasians, 4.5% Asian, and 5.2% Black (**Table 1**). A higher proportion were genotype-positive, a lower proportion were familial, a higher proportion had non-sustained VT, and had higher LA diameter z-scores at baseline. The type of SCD events are shown in **Supplemental Figure IV**. The cumulative proportion of SCD events at 1-year follow-up was 2.3% [0.5%, 4.1%], and at 5 years was 6.8% [3.2%, 10.3%] with a total of 22 SCD events over a median follow-up of 3.3 [1.3-7.0] years (**Figure 1b**). The incidence of SCD events was not significantly different from the discovery cohort ( $p=0.57$ ). Patients in the replication cohort were scored using both risk prediction models and performance of each model in the validation cohort was assessed. The c-statistic was 0.707 for the clinical model, and 0.724 for the clinical/genetic model with acceptable agreement between the predicted and observed 5-year cumulative proportion of SCD events for both models.

## Discussion

The incidence of sudden cardiac death in pediatric HCM is significantly higher than in adults.<sup>28</sup> The 5-year risk of a SCD event in our study was 9.1%. However, only 25% received an ICD that was able to abort the event. The remaining patients either died without an ICD or received an ICD only after experiencing the event. In addition, of the 102 patients in the cohort who received a primary prevention ICD, 86% did not receive an appropriate shock including many who had a 5-year follow-up. This is comparable to adult studies and highlights a major gap in knowledge on how to risk stratify for sudden death in the pediatric population.<sup>36, 14, 37</sup> The practice guidelines to date have relied on adult markers for risk stratifying children and adolescents.<sup>4</sup> Using data from a multi-center consortium of pediatric HCM centers, we found important differences in risk factors between children and adults. Using age-specific risk factors, we developed and validated a pediatric SCD risk prediction model that can bridge this gap in knowledge and provide the evidence needed by clinicians to assist in decision making for SCD prevention. Currently, only 1 in 9 prophylactic ICDs are appropriate implantations.<sup>38</sup> The use of a prediction tool has the potential to increase appropriate ICD implantation while reducing unwanted ICD implantation in a vulnerable population that is at higher risk of ICD complications due to their small size and physiological differences from adults.

To develop this model, we employed an evidence-based approach to determine whether the conventional risk factors for SCD identified mostly through adult studies apply to children. Our analysis confirmed the positive association of age, history of syncope, non-sustained VT, LV wall thickness and LA diameter with SCD risk but also revealed some important differences between pediatric and adult risk factors. For example, while there was a linear relationship between septal thickness and SCD risk, the risk plateaued with massive septal hypertrophy



suggesting that unlike adults, there was no clear septal z-score threshold that conferred an independent risk of SCD. Also, there was no significant association between peak resting LVOT gradient with SCD, and there was an inverse association with SCD at very high gradients. This was likely not related to medication use since SCD event frequency was not different by beta-blocker use. It is not clear if this could be related to a possible protective effect of septal myectomy in patients with high gradients.<sup>9, 39</sup> The finding of a positive association of age with SCD risk is consistent with the known higher penetrance of SCD in adolescents and teenagers.<sup>7</sup> The overall lower frequency of SCD in early onset cases may also be related in part to a lower survival into teenage years due to a higher non-SCD mortality and transplant in early life. The difference in outcomes is unlikely to be related to the presence of non-sarcomeric gene variants in younger patients (all of whom had isolated HCM at the time of diagnosis and follow-up) since non-sarcomeric gene variants accounted for less than 3% of early onset cases. In fact, our previous work has shown that sarcomeric genotype itself can influence disease onset and severity with the affected sarcomeric gene, variant burden and de novo status associated with earlier onset HCM and lower freedom from not just SCD but also need for myectomy, transplant or death.<sup>40</sup>

We noted that a family history of SCD did not emerge as a significant risk factor which may be so for several reasons including the often sporadic occurrence of childhood HCM, a higher likelihood that SCD events may not have manifested yet in young adult relatives of child probands, and the limitation in tracking all family SCD events in a retrospective study design. Further, family history may be protective as it prompts screening, early diagnosis and timely follow-up and interventions in family members. The lack of statistically significant associations

between family history of SCD and LVOT gradient with SCD risk in childhood HCM is consistent with other recently published reports.<sup>7, 41-43</sup>

Prior studies have reported that patients carrying at least one pathogenic/likely pathogenic variant were more likely to experience earlier disease onset and worse patient outcomes.<sup>10, 23, 24, 40, 44, 45</sup> This aligns with our finding that genotype-positive individuals had a 1.3-fold higher risk of experiencing a SCD event when compared to individuals who were genotype-negative on genetic testing after accounting for all clinical risk factors. In a first attempt to incorporate genetic risk into the prediction model, we observed only a modest difference in prediction accuracy between the clinical and combined models. The failure to see a larger difference may be related to the limited uptake of genetic testing whereby only 54% patients had undergone genetic testing with less than a third being genotype positive. We also explored the effect of incorporating affected gene and variant burden into the model but were likely underpowered to identify meaningful genotype-specific differences in SCD risk. Larger studies are needed to analyze and incorporate genotype-specific differences in risk predictions.

Finally, our model provided a good prediction accuracy with a c-statistic of 0.75 which was higher when compared to a recent study in a UK cohort where the c-statistic was 0.69 in the training set with no external validation.<sup>28</sup> The UK study included 5 pre-selected risk factors that were not re-evaluated prior to inclusion in the model. Their model did not include age at diagnosis, and did not differentiate between IVSD and LVPWD z-scores as independent predictors of SCD risk but instead used maximal LV wall thickness in any segment. We re-evaluated all potential risk factors to ensure that all evidence-based risk factors were included and the non-linear relationship of the risk factors with SCD risk was incorporated into the model to improve its accuracy. Importantly, we were able to externally validate the clinical as well as

clinical/genetic models using an independent cohort. The predictive accuracy of both models remained higher than 0.7 which is comparable in performance to the adult SCD risk calculator in clinical use.<sup>18</sup> The decrease in c-statistic in the validation cohort may have been related to a non-significantly lower SCD event rate due to a potential survivor bias since the SHaRe validation cohort was comprised predominantly of adult age survivors of childhood onset HCM.

### **Clinical significance**

There is important potential for our findings to assist in clinical decision-making to prevent one of the most tragic outcomes of pediatric HCM. Our study reports the only independently validated model for SCD risk prediction in pediatric HCM, and the only study that provides evidence from a large ethnically and geographically relevant North American pediatric cohort.

Our findings reinforce that most SCD risk factors are not binary and that, in children, the decision for ICD should not be made on the basis of a single risk factor especially given the higher ICD complication rates in this age group. The model ensures that all validated risk factors are considered in the decision making process using an unbiased approach.<sup>46</sup> The algorithm we have developed not only encapsulates practice recommendations but also provides an individualized estimate of 5-year sudden death risk that can be used in ICD shared decision making between patient and provider as opposed to a binary classification of high versus low risk. The ACC/AHA guidelines include the following Class I recommendation, highlighting the emphasis on shared decision making for ICD between patients and providers: *“The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits and risks to allow the informed patient’s active participation in decision making”*.<sup>4</sup> Ultimately, this model has the potential for use as a decision support tool to facilitate ICD shared decision making through

individualized risk prediction, and improve clinical outcomes through appropriate ICD use in high-risk patients.

### **Limitations**

(i) The study has limitations inherent to any retrospective analysis i.e. missing data, survivor bias, and lower uptake of genetic testing in the earlier era. Missing echocardiographic data was addressed through a re-review of echocardiograms where available and through imputation where this was not possible. We deliberately did not perform an echocardiographic core laboratory analysis since a real world, point of care tool has to rely on locally acquired data. We did however standardize the calculations for z-score measurements. (ii) Our study did not include emerging risk factors like late gadolinium enhancement on cardiac MRI due to challenges related to low yield of late gadolinium enhancement in children, lack of a clear definition for an abnormal cut-off especially in children, variability in cardiac MRI use across centers, and the inability to perform this test in younger children without sedation that limits universal clinical use at this time. Atypical ventricular phenotypes such as apical aneurysm formation which are rare in pediatric HCM were also not included as risk factors. (iii) While some patients harbored variants in non-sarcomeric genes like RASopathy-associated genes, we confirmed that patients were non-syndromic at the time of clinical ascertainment and did not have a phenotype consistent with a syndromic, metabolic or neuromuscular phenotype. (iv) We recognize that some appropriate ICD discharges may have been for self-terminating VT/VF which can overestimate SCD. Anti-tachycardia pacing events were also not captured. (v) Despite an acceptable predictive accuracy of our model at present, we recognize that childhood and adolescence are times of significant dynamic change in cardiac growth, and phenotypic



expression. Future iterations of the model will need to be dynamic and incorporate the trajectory of phenotypic change in HCM with time to further improve prediction accuracy.

### **Conclusions**

The independently validated PRIMaCY model has over 70% accuracy for SCD risk prediction in pediatric HCM. We anticipate that clinical uptake of this model of risk prediction will improve the application of clinical practice guidelines, facilitate shared decision making around ICD implantation through individualized risk prediction, and improve clinical outcomes through appropriate ICD use in high risk pediatric patients while avoiding ICDs in low risk patients. An important future goal will be to incorporate this model into hospital electronic health systems as a point of care tool for physicians and to assess the implementation effectiveness of this approach in the application of clinical practice guidelines.



### **Acknowledgments**

None.

### **Sources of Funding**

The project was supported through funding from the Ted Rogers Centre for Heart Research, and the Heart and Stroke Foundation / Robert M Freedom Chair to Dr. Mital. Dr. Ingles was supported by a National Health and Medical Research Council (NHMRC) Career Development Fellowship (#1162929). Dr. Semsarian was supported by an NHMRC Practitioner Fellowship (#1154992).

## Disclosures

Dr. Balaji is a consultant for Milestone Pharmaceuticals and is on the medical advisory board for Yor Labs. Dr. Conway is a Medical Monitor for the Pumpkin Trial and has received unrestricted education funding from Abbott. Dr. Rossano is a consultant for Amgen, Bayer, Novartis, and CLS Behring. Dr. Kantor is a consultant for Novartis, and Astra-Zeneca. Drs. Colan, Ingles, Olivotto, Russell and Ho received research grant support and/or consultation fees from Myokardia Inc.

## Supplemental Materials

Supplemental Figures I-IV

Supplemental Tables I-II



## Authors

Anastasia Miron, HBA<sup>1</sup>; Myriam Lafreniere-Roula, PhD<sup>2</sup>; Chun-Po Steve Fan, PhD, P.Stat<sup>2</sup>;  
 Katey R. Armstrong, MBChB, MD<sup>3</sup>; Andreea Dragulescu, MD, PhD<sup>4</sup>; Tanya Papaz, HBA<sup>1</sup>;  
 Cedric Manlhiot, PhD<sup>5</sup>; Beth Kaufman, MD<sup>6</sup>; Ryan J. Butts, MD<sup>7</sup>; Letizia Gardin, MD<sup>8</sup>;  
 Elizabeth A. Stephenson, MD<sup>9</sup>; Taylor S. Howard, MD<sup>10</sup>; Pete F. Aziz, MD<sup>11</sup>;  
 Seshadri Balaji, MBBS, MRCP(UK), PhD<sup>12</sup>; Virginie Beauséjour Ladouceur, MD<sup>4</sup>;  
 Lee N. Benson, MD<sup>4</sup>; Steven D. Colan, MD<sup>13</sup>; Justin Godown, MD<sup>14</sup>;  
 Heather T. Henderson, MD<sup>15</sup>; Jodie Ingles, PhD, MPH<sup>16</sup>; Aamir Jeewa, MD<sup>4</sup>;  
 John L. Jefferies, MD, MPH<sup>17</sup>; Ashwin K. Lal, MD<sup>18</sup>; Jacob Mathew, MBBS FRACP<sup>19</sup>;  
 Emilie Jean-St-Michel, MD CM, MSc<sup>4</sup>; Michelle Michels, MD, PhD<sup>20</sup>;  
 Stephanie J. Nakano, MD<sup>21</sup>; Iacopo Olivotto, MD<sup>22</sup>; John J. Parent, MD, MS<sup>23</sup>;

Alexandre C. Pereira, MD, PhD<sup>24</sup>; Christopher Semsarian, MBBS, PhD, MPH<sup>16</sup>;  
 Robert D. Whitehill, MD<sup>25</sup>; Samuel G. Wittekind, MD, MSc<sup>26</sup>; Mark W. Russell, MD<sup>27</sup>;  
 Jennifer Conway, MD<sup>28</sup>; Marc E. Richmond, MD, MS<sup>29</sup>; Chet Villa, MD<sup>26</sup>;  
 Robert G. Weintraub, MBBS<sup>19,30</sup>; Joseph W. Rossano, MD<sup>31</sup>; Paul F. Kantor, MBCh<sup>32</sup>;  
 Carolyn Y. Ho, MD<sup>33</sup>; Seema Mital, MD<sup>1,9</sup>

<sup>1</sup>Division of Cardiology, Hospital for Sick Children, Toronto, ON, Canada; <sup>2</sup>Ted Rogers Computational Program, Ted Rogers Centre for Heart Research, The Hospital for Sick Children, University Health Network, Toronto, ON, Canada; <sup>3</sup>Division of Pediatric Cardiology, Department of Pediatrics, BC Children's Hospital, Vancouver, BC, Canada; <sup>4</sup>Department of Cardiology, Hospital for Sick Children, Toronto, ON, Canada; <sup>5</sup>Department of Pediatrics, Johns Hopkins Medical Center, Baltimore, MD; <sup>6</sup>Department of Pediatrics, Lucile Packard Children's Hospital Stanford, Palo Alto, CA; <sup>7</sup>Division of Pediatric Cardiology, Department of Pediatrics, Children's Medical Center of Dallas, Dallas, TX; <sup>8</sup>Department of Cardiology, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada; <sup>9</sup>Department of Cardiology, Labatt Family Heart Centre, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; <sup>10</sup>Department of Pediatrics, Section of Pediatric Cardiology, Baylor College of medicine, Texas Children's Hospital, Houston, TX; <sup>11</sup>Center for Pediatric and Congenital Heart Disease, Pediatric Electrophysiology and Pacing, Cleveland Clinic Children's Hospital, Cleveland, OH; <sup>12</sup>Department of Pediatrics, Division of Cardiology, Oregon health & Science University, OHSU Doernbecher Children's Hospital, Portland, OR; <sup>13</sup>Department of Cardiology, Boston Children's Hospital, Boston, MA; <sup>14</sup>Department of Pediatrics, Division of Pediatric Cardiology, Monroe Carrell Jr Children's Hospital at Vanderbilt, Nashville, TN; <sup>15</sup>Pediatrics, Medical University of

South Carolina, Charleston, SC; <sup>16</sup>Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, NSW, Australia; <sup>17</sup>Division of Adult Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN; <sup>18</sup>Division of Pediatric Cardiology, University of Utah Primary Children's Hospital, Salt Lake City, UT; <sup>19</sup>Department of Cardiology, The Royal Children's Hospital, Melbourne, VIC, Australia; <sup>20</sup>Department of Cardiology, Thoraxcenter, Erasmus MC Rotterdam, Rotterdam, ZH, Netherlands; <sup>21</sup>Department of Pediatrics, Division of Cardiology, Children's Hospital Colorado, Aurora, CO; <sup>22</sup>Referral Center for Cardiomyopathies, Careggi University Hospital, Florence, FI, Italy; <sup>23</sup>Department of Pediatrics, Riley Children's Hospital, Indianapolis, IN; <sup>24</sup>Laboratory of Genetics and Molecular Cardiology, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, SP, Brazil; <sup>25</sup>Division of Cardiology, Children's Healthcare of Atlanta, Atlanta, GA; <sup>26</sup>The Heart Institute, Cincinnati Children's Hospital, Cincinnati, OH; <sup>27</sup>Pediatrics, C.S. Mott Children's Hospital, Ann Arbor, MI; <sup>28</sup>Division of Pediatric Cardiology, Department of Pediatrics, Stollery Children's Hospital, Edmonton, AB, Canada; <sup>29</sup>Division of Pediatric Cardiology, Department of Pediatrics, Columbia University College of Physicians and Surgeons/Morgan Stanley Children's Hospital, New York, NY; <sup>30</sup>Murdoch Children's Research Institute, University of Melbourne, Melbourne, VIC, Australia; <sup>31</sup>Division of Cardiology, Children's Hospital of Philadelphia, PA; <sup>32</sup>Division of Cardiology, Children's Hospital of Los Angeles, Los Angeles, CA; <sup>33</sup>Cardiovascular Division, Brigham and Women's Hospital, Boston, MA

## References

1. Liew AC, Vassiliou VS, Cooper R, Raphael CE. Hypertrophic Cardiomyopathy-Past, Present and Future. *J Clin Med.* 2017;6:118.



2. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of Hypertrophic Cardiomyopathy in a General Population of Young Adults. *Circulation*. 1995;92:785-789.
3. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2015;65:1249-1254.
4. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;58:e212-e260.
5. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and Mechanistic Insights Into the Genetics of Cardiomyopathy. *J Am Coll Cardiol*. 2016;68:2871-2886.
6. O'Mahony C, Tome Esteban MT, Lambiase P, Pantazis A, Dickie S, McKenna W, Elliott P. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Heart*. 2013;99:534-541.
7. Norrish G, Ding T, Field E, McLeod K, Iliina M, Stuart G, Bhole V, Uzun O, Brown E, Daubeney PEF et al. A validation study of the European Society of Cardiology guidelines for risk stratification of sudden cardiac death in childhood hypertrophic cardiomyopathy. *Europace*. 2019;21:1559-1565.
8. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes NAM, Shannon KM, Ashley EA, Day SM, Pacileo G et al. Prevention of Sudden Cardiac Death With Implantable Cardioverter-Defibrillators in Children and Adolescents With Hypertrophic Cardiomyopathy. *J Am Coll Cardiol*. 2013;61:1527-1535.
9. Nakano SJ, Menon SC. Risk stratification in pediatric hypertrophic cardiomyopathy: Insights for bridging the evidence gap? *Prog Pediatr Cardiol*. 2018;49:31-37.
10. Maurizi N, Passantino S, Spaziani G, Girolami F, Arretini A, Targetti M, Pollini I, Tomberli A, Pradella S, Calabri GB et al. Long-term Outcomes of Pediatric-Onset Hypertrophic Cardiomyopathy and Age-Specific Risk Factors for Lethal Arrhythmic Events. *JAMA Cardiol*. 2018;3:520-525.
11. Krause U, Müller MJ, Wilberg Y, Pietzka M, Backhoff D, Ruschewski W, Paul T. Transvenous and non-transvenous implantable cardioverter-defibrillators in children, adolescents, and adults with congenital heart disease: Who is at risk for appropriate and inappropriate shocks? *Europace*. 2018;21:106-113.
12. Kaski JP, Tomé Esteban MT, Lowe M, Sporton S, Rees P, Deanfield JE, McKenna WJ, Elliott PM. Outcomes after implantable cardioverter-defibrillator treatment in children with hypertrophic cardiomyopathy. *Heart*. 2007;93:372.
13. DeWitt ES, Triedman JK, Cecchin F, Mah DY, Abrams DJ, Walsh EP, Gauvreau K, Alexander ME. Time Dependence of Risks and Benefits in Pediatric Primary Prevention Implantable Cardioverter-Defibrillator Therapy. *Circ Arrhythm Electrophysiol*. 2014;7:1057-1063.

14. Maron BJ, Casey SA, Olivotto I, Sherrid MV, Semsarian C, Autore C, Ahmed A, Boriani G, Francia P, Winters SL et al. Clinical Course and Quality of Life in High-Risk Patients With Hypertrophic Cardiomyopathy and Implantable Cardioverter-Defibrillators. *Circ Arrhythm Electrophysiol.* 2018;11:e005820.
15. Prinz C, Vogt J, Bitter T, Muntean BG, Hering D, Horstkotte D, Faber L. Incidence of adequate ICD interventions in patients with hypertrophic cardiomyopathy supposed to be at high risk for sudden cardiac death. *Acta Cardiol.* 2010;65:521-525.
16. Iwai S. Sudden Cardiac Death Risk Stratification and the Role of the Implantable Cardiac Defibrillator. *Cardiol Clin.* 2019;37:63-72.
17. Berul CI, Van Hare GF, Kertesz NJ, Dubin AM, Cecchin F, Collins KK, Cannon BC, Alexander ME, Triedman JK, Walsh EP et al. Results of a Multicenter Retrospective Implantable Cardioverter-Defibrillator Registry of Pediatric and Congenital Heart Disease Patients. *J Am Coll Cardiol.* 2008;51:1685-1691.
18. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I et al. International External Validation Study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). *Circulation.* 2018;137:1015-1023.
19. 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.* 2013;35:2010-2020.
20. Maron M, Rowin E, Maron BJ. Increasing evidence that risk scores underperform in predicting sudden death in hypertrophic cardiomyopathy. *Heart.* 2019;105:1850.
21. O'Mahony C, Akhtar MM, Anastasiou Z, Guttman OP, Vriesendorp PA, Michels M, Magri 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.* 2019;105:623-631.
22. Armstrong K, Jeon J, Fan Chun-Po S, Manlhiot C, Wilson J, George K, Stephenson E, Mital S. Abstract 17056: Validation of the Adult Hypertrophic Cardiomyopathy Sudden Death Risk Calculator in a Pediatric Population. *Circulation.* 2016;134:A17056-A17056.
23. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation.* 2018;138:1387-1398.
24. Kelly M, Semsarian C. Multiple Mutations in Genetic Cardiovascular Disease. *Circ Cardiovasc Genet.* 2009;2:182-190.
25. Leong KMW, Chow J-J, Ng FS, Falaschetti E, Qureshi N, Koa-Wing M, Linton NWF, Whinnett ZI, Lefroy DC, Davies DW et al. Comparison of the Prognostic Usefulness of the European Society of Cardiology and American Heart Association/American College of Cardiology Foundation Risk Stratification Systems for Patients with Hypertrophic Cardiomyopathy. *Am J Cardiol.* 2018;121:349-355.
26. Maron MS, Rowin EJ, Maron BJ. The ESC Risk Score Is Less Reliable than ACC/AHA Risk Factors in Hypertrophic Cardiomyopathy: When Sensitivity Trumps Specificity. *Can J Cardiol.* 2019;35:1626-1628.
27. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, Koethe BC, Romashko M, Link MS, Maron BJ. Enhanced American College of

- Cardiology/American Heart Association Strategy for Prevention of Sudden Cardiac Death in High-Risk Patients With Hypertrophic Cardiomyopathy. *JAMA Cardiol.* 2019;4:644-657.
28. Norrish G, Ding T, Field E, Ziólkowska L, Olivotto I, Limongelli G, Anastasakis A, Weintraub R, Biagini E, Ragni L et al. Development of a Novel Risk Prediction Model for Sudden Cardiac Death in Childhood Hypertrophic Cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol.* 2019;4:918-927.
  29. Colan SD. Normal Echocardiographic Values for Cardiovascular Structures. *Echocardiography in Pediatric and Congenital Heart Disease.* 2016:883-901.
  30. Sluysmans T, Colan SD. Structural Measurements and Adjustments for Growth. *Echocardiography in Pediatric and Congenital Heart Disease.* 2016:61-72.
  31. 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;17:405-424.
  32. Wreede L, Fiocco M, Putter H. Mstate: An R Package for the Analysis of Competing Risks and Multi-State Models. *J Stat Softw.* 2011;38:1-30.
  33. Heymans MW, van Buuren S, Knol DL, van Mechelen W, de Vet HCW. Variable selection under multiple imputation using the bootstrap in a prognostic study. *BMC Med Res Methodol.* 2007;7:33-33.
  34. Graham JW. Imputation in Practice. In *Flexible Imputation of Missing Data. Advanced Techniques Part 2. Second Edition.* Editor: Van Buuren S. CRC Press, Taylor & Francis Group; 2018.
  35. Wolbers M, Blanche P, Koller MT, Witteman JCM, Gerds TA. Concordance for prognostic models with competing risks. *Biostatistics.* 2014;15:526-539.
  36. Trivedi A, Knight BP. ICD Therapy for Primary Prevention in Hypertrophic Cardiomyopathy. *Arrhythm Electrophysiol Rev.* 2016;5:188-196.
  37. Maron BJ, Spirito P, Shen W-K, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T et al. Implantable Cardioverter-Defibrillators and Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy. *JAMA.* 2007;298:405-412.
  38. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RHM, Garberich RF, Udelson JE, Maron MS. Hypertrophic Cardiomyopathy in Adulthood Associated With Low Cardiovascular Mortality With Contemporary Management Strategies. *J Am Coll of Cardiol.* 2015;65:1915-1928.
  39. Javidgonbadi D, Andersson B, Abdon N-J, Schaufelberger M, Östman-Smith I. Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: Probable dose-related protection from beta-blocker therapy. *Open Heart.* 2019;6:e000963.
  40. Mathew J, Zahavich L, Lafreniere-Roula M, Wilson J, George K, Benson L, Bowdin S, Mital S. Utility of genetics for risk stratification in pediatric hypertrophic cardiomyopathy. *Clin Genet.* 2018;93:310-319.
  41. Balaji S, DiLorenzo MP, Fish FA, Etheridge SP, Aziz PF, Russell MW, Tisma S, Pflaumer A, Sreeram N, Kubus P et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: An international multicenter study. *Heart Rhythm.* 2019;16:1462-1467.

42. Bittencourt MI, Cader SA, Araújo DV, Salles ALF, Albuquerque FN, Spinetti PPM, Albuquerque DC, Mourilhe-Rocha R. Role of Myocardial Fibrosis in Hypertrophic Cardiomyopathy: A Systematic Review and Updated Meta-Analysis of Risk Markers for Sudden Death. *Arq Bras Cardiol.* 2019;112:281-289.
43. Alexander PMA, Nugent AW, Daubeney PEF, Lee KJ, Sleeper LA, Schuster T, Turner C, Davis AM, Semsarian C, Colan SD et al. Long-Term Outcomes of Hypertrophic Cardiomyopathy Diagnosed During Childhood. *Circulation.* 2018;138:29-36.
44. Noseworthy PA, Newton-Cheh C. Genetic Determinants of Sudden Cardiac Death. *Circulation.* 2008;118:1854-1863.
45. Kaski JP, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, McKenna WJ, Elliott PM. Prevalence of Sarcomere Protein Gene Mutations in Preadolescent Children With Hypertrophic Cardiomyopathy. *Circ Cardiovasc Genet.* 2009;2:436-441.
46. Weissler-Snir A, Adler A, Williams L, Gruner C, Rakowski H. Prevention of sudden death in hypertrophic cardiomyopathy: Bridging the gaps in knowledge. *Eur Heart J.* 2016;38:1728-1737.



# Circulation

**Table 1.** Clinical characteristics of the PRIMaCY and SHaRe cohorts

	Number ascertained	Variable* (PRIMaCY)	Number ascertained	Variable* (SHaRe)	P-value
Age at first evaluation (years)	572	9.8 (2.1 – 13.9)	285	13.8 (8.3 – 16.2)	<0.001
Sex (Male)	572	394 (68.9%)	285	199 (69.8%)	0.81
Genetic testing done	572	311 (54.4%)	285	166 (58.2%)	0.315
Genetic testing results	311		166		0.024
Positive		160 (51.4%)		108 (65.0%)	
Inconclusive		66 (21.2%)		27 (16.3%)	
Negative		85 (27.3%)		31 (18.7%)	
Family history of HCM	550	264 (48.0%)	285	102 (35.8%)	<0.001
Family history of SCD	572	105 (18.4%)	206	29 (14.1%)	0.196
Documented non-sustained VT	572	18 (3.1%)	88	7 (8%)	0.037
History of unexplained syncope	572	17 (3.0%)	285	6 (2.1%)	0.51
Received beta blocker	565	336 (59.1%)	284	127 (44.7%)	<0.001
<b>Echocardiographic features at diagnosis</b>			<b>N</b>	<b>Statistic</b>	
IVSD z-score	572	9.5 (5.0 – 16.8)	283	9.4 (4.7 – 16.7)	0.66
LVPWD z-score	566	2.4 (0.3 – 5.0)	269	2.4 (0.6 – 4.9)	0.43
LA diameter z-score	453	1.1 (0.1 – 2.1)	190	1.4 (0.3 – 2.5)	0.035
Peak resting LVOT gradient (mm Hg)	401	13 (0.0 – 46.0)	90	10 (7 – 18)	0.81
LVOT obstructed (qualitative)	121	19 (16%)	175	40 (23%)	0.141
<b>Survival outcomes</b>			<b>N</b>	<b>Statistic</b>	
SCD events	572	53 (9.3%)	285	22 (7.7%)	<0.001
SCD	572	14 (2.4%)	285	8 (2.8%)	
Resuscitated SCA	572	25 (4.4%)	285	9 (3.2%)	
Appropriate shock with prophylactic ICD	572	14* (2.4%)	285	5 (1.8%)	
<b>Incidence rate†</b>			<b>N</b>	<b>Statistic</b>	
Years from diagnosis	572	3.9 (1.5, 6.7)	285	3.9 (1.6 – 7.4)	
Patient-years of follow-up	572	2855	285	1400	
<b>Outcomes</b>					
Event-free	572	17.9	285	18.3	
SCD event	572	1.9	285	1.6	
Non SCD death	572	3.2	285	0.5	

\* Continuous variables were summarized using median and IQR; categorical variables were summarized using frequencies and proportions

† Incidence rate = Events per 100 patient-years of follow-up

PRIMaCY, Precision Medicine for Cardiomyopathy; SHaRe, Sarcomeric Human Cardiomyopathy Registry; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; VT, ventricular tachycardia; IVSD, inter-ventricular septal diameter; LVPWD, left ventricular posterior wall diameter; LA, left atrial; LV, left ventricle; LVOT, left ventricular outflow tract; SCD, sudden cardiac death; SCA, sudden cardiac arrest; ICD, implantable cardioverter defibrillator

**Table 2.** Categorical predictors of 5-year sudden cardiac death risk

<b>Clinical model</b>	<b>Hazard ratios [95% CI]</b>
Prior history of non-sustained VT	2.87 [1.00, 6.57]
Prior history of syncope	7.40 [1.21, 32.81]
<b>Clinical/genetic model</b>	
Prior history of non-sustained VT	2.58 [1.00, 6.17]
Prior history of syncope	7.23 [1.09, 33.57]
Pathogenic variant in any gene (reference: confirmed absence of variant)	1.32 [1.00, 2.12]

CI, confidence interval; VT, ventricular tachycardia



Circulation

**Table 3.** Observed versus model-predicted 5-year freedom from sudden cardiac death (n=572)

Risk group categories	Risk tertile	Average predicted risk	Observed risk [95% CI]	c-statistic
<b>Clinical model</b>				
low risk	< 4.7%	3.4%	2.8% [1.1%, 7.6%]	0.750
medium risk	4.7% - 8.3%	6.3%	7.2% [3.9%, 13.4%]	
high risk	> 8.3%	20.0%	18.5% [12.7%, 26.9%]	
<b>Clinical + genetic model</b>				
low risk	< 4.7%	3.3%	1.9% [0.6%, 5.9%]	0.762
medium risk	4.7% - 8.3%	6.2%	7.6% [4.1%, 14.1%]	
high risk	> 8.3%	20.0%	18.8% [13.1%, 27.1%]	

CI, confidence intervals



# Circulation

## Figure Legends

**Figure 1. Cumulative proportion of SCD events estimated using competing risk models in PRIMaCY and SHaRe cohorts.** PRIMaCY cohort (n=572): The cumulative proportion [95% CI] of SCD events in pediatric HCM patients at 1-year follow-up was 2.8% [1.4%, 4.2%], at 5 years was 9.1% [6.3%, 11.9%], and at 10 years was 15.0% [10.0%, 19.7%]. The cumulative proportion of death from other causes at 1-year follow-up was 0.9% [0.1%, 1.8%], at 5 years was 1.8% [0.6%, 3.0%], and at 10 years was 1.8% [0.6%, 3.0%]. **b.** SHaRE cohort (n=285): The cumulative proportion [95% CI] of SCD events at 1-year follow-up was 2.3% [0.5%, 4.1%], at 5 years was 6.8% [3.2%, 10.3%], and at 10 years was 13.7% [6.5%, 20.4%]. The cumulative proportion of death from other causes at 1-year follow-up was 0.7% [0.0%, 1.7%], at 5 years was 2.1% [0.2%, 3.9%], and at 10 years was 4.5% [0.6%, 8.2%]. PRIMaCY, Precision Medicine for Cardiomyopathy Study; SHaRe, Sarcomeric Human Cardiomyopathy Registry; SCD, sudden cardiac death; HCM, hypertrophic cardiomyopathy

**Figure 2. Regression-adjusted effects of continuous co-variates and clinical SCD risk prediction model performance (n=572).** (a-e) The top of each figure shows the observed values of the continuous risk predictor among pediatric HCM patients in the training cohort who experienced the composite SCD outcome, the bottom shows the observed values of the predictor among those who did not experience the composite SCD outcome. SCD risk increased with **a)** age at diagnosis; **b)** increase in IVSD z-score; **c)** LVPWD z-score; and **d)** LA diameter z-score; **e)** The risk associated with peak resting LVOT gradient remained flat when the gradient was  $\leq 100$  mmHg and decreased as the gradient increased above 100 mmHg; **f)** Cumulative



proportion of SCD-events stratified by tertiles of risk predicted by the clinical only model i.e. predicted risk below 4.7%, 4.7%-8.3%, and above 8.3%; **g)** The calibration curve for the clinical model applied to the training cohort shows the predicted versus the observed five-year risk of the composite SCD outcome. The prediction accuracy i.e. c-statistic of the model was 0.75. The dashed line, the 45° line through 0, represents a perfectly calibrated model between the observed and the predicted 5-year survival probabilities.

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; IVSD, inter-ventricular septal diameter; LVPWD, left ventricular posterior wall diameter; LA, left atrium; LVOT, LV outflow tract

**Figure 3. Regression-adjusted effects of continuous covariates and clinical/genetic SCD risk prediction model performance (n=572).** (a-e) The top of each figure shows the observed values of the continuous risk predictor among pediatric HCM patients in the training cohort who experienced the composite SCD outcome, the bottom shows the observed values of the predictor among those who did not experience the composite SCD outcome. SCD risk increased with **a)** age at first evaluation; **b)** increase in IVSD z-score; **c)** LVPWD z-score; and **d)** LA diameter z-score; **e)** The risk associated with peak resting LV outflow tract gradient remained flat when the gradient was  $\leq 100$  mmHg and decreased as the gradient increased above 100 mmHg; **f)** Cumulative proportion of SCD-events stratified by tertiles of risk predicted by the clinical/genetic model i.e. predicted risk below 4.7%, 4.7%-8.3%, and above 8.3%; **g)** The calibration curve for the clinical/genetic model applied to the training cohort shows the predicted versus the observed five-year risk of the composite SCD outcome. The prediction accuracy i.e. c-

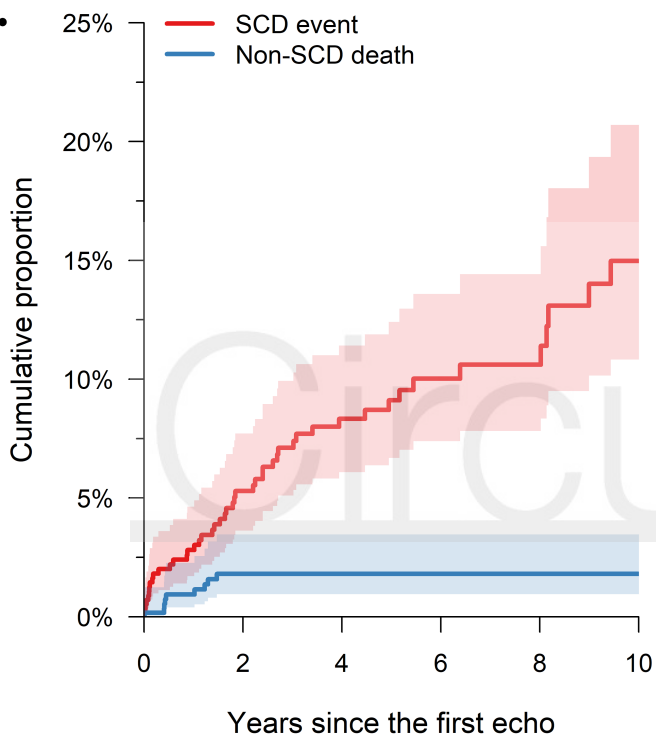
statistic of the model was 0.762. The dashed line, the 45° line through 0, represents a perfectly calibrated model between the observed and the predicted 5-year survival probabilities.

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; IVSD, inter-ventricular septal diameter; LVPWD, left ventricular posterior wall diameter; LA, left atrium; LVOT, LV outflow tract



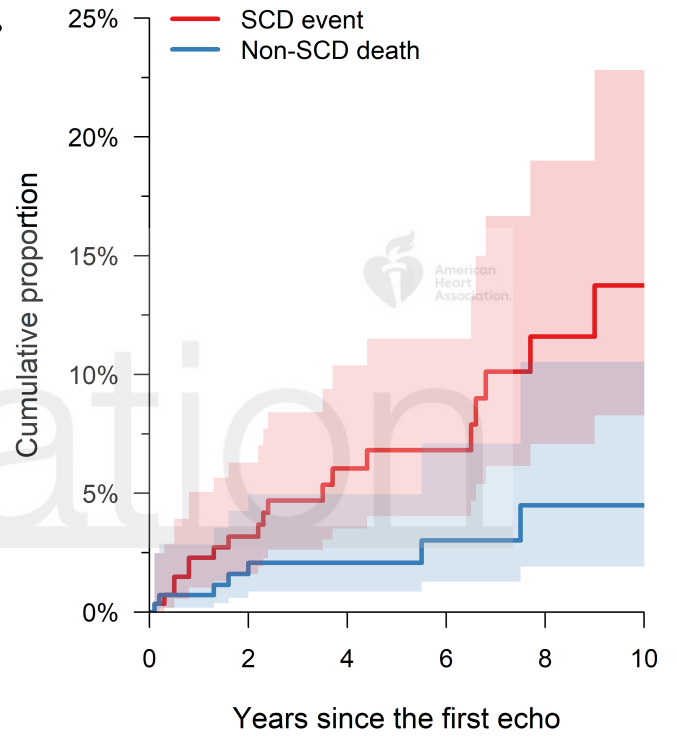
# Circulation

a.

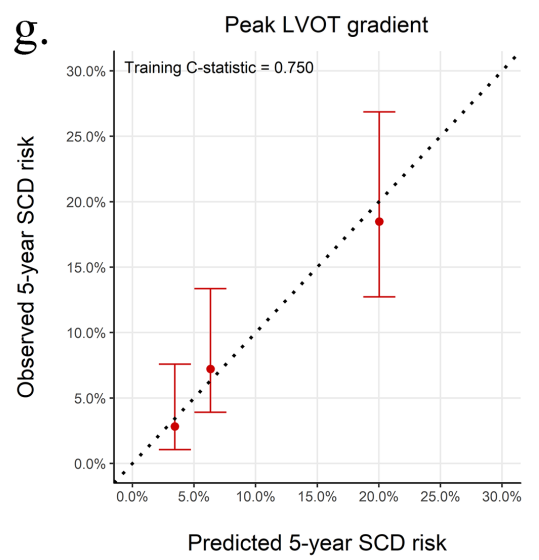
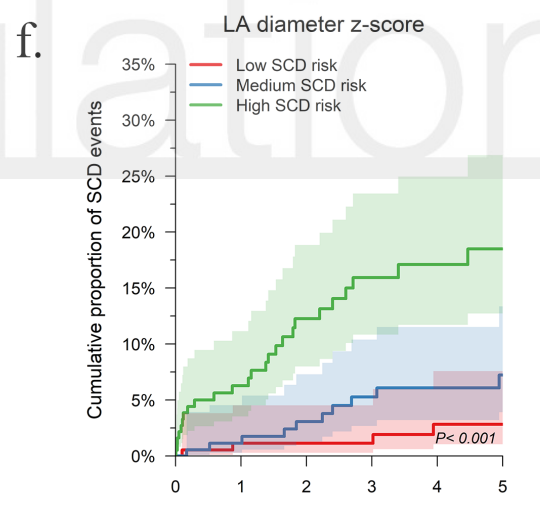
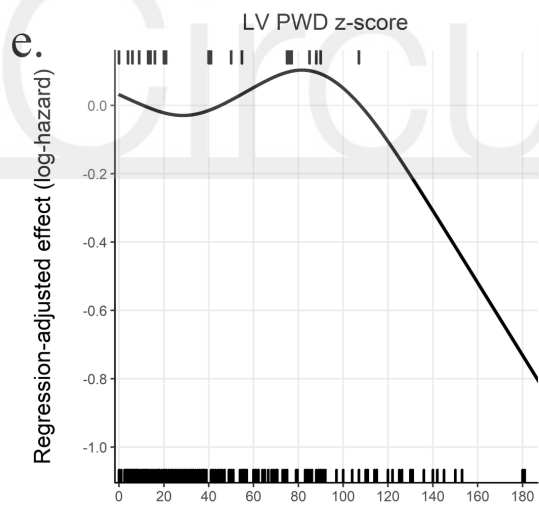
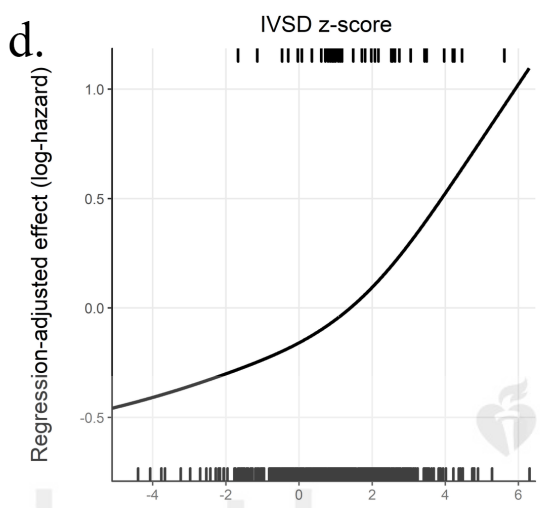
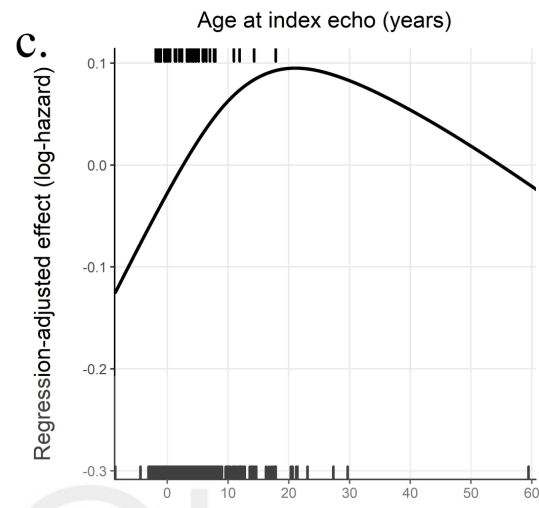
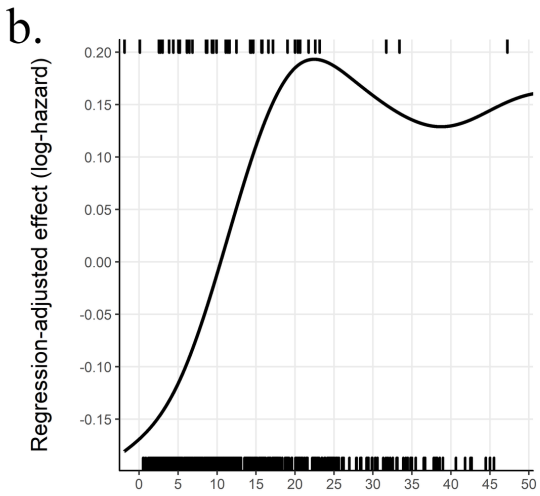
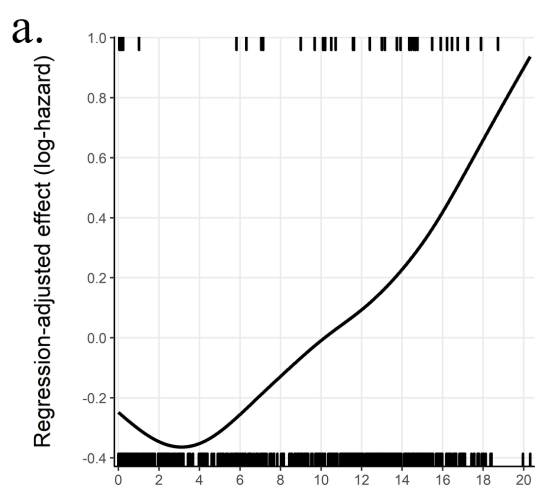


At-risk: 572 385 265 162 112 80

b.



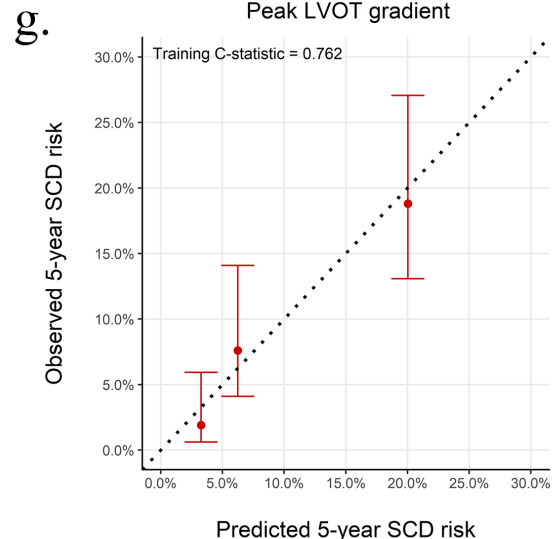
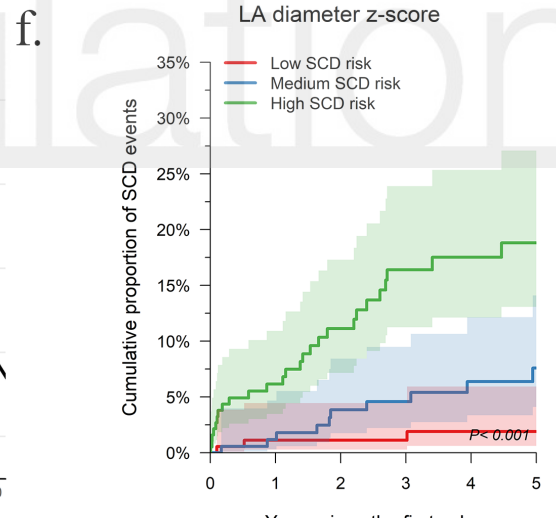
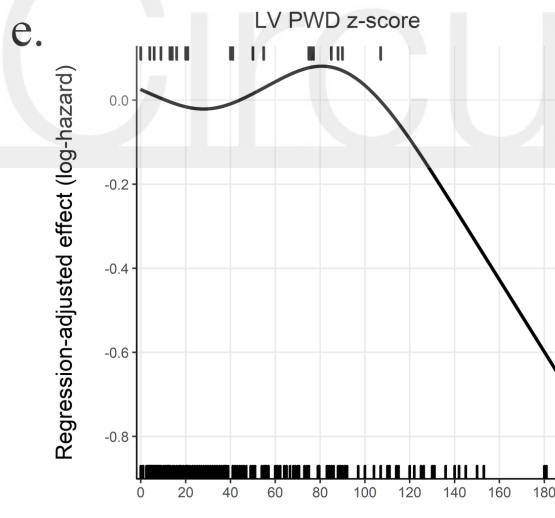
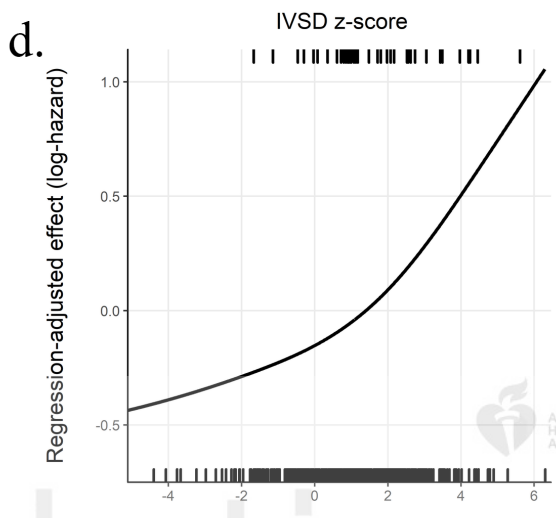
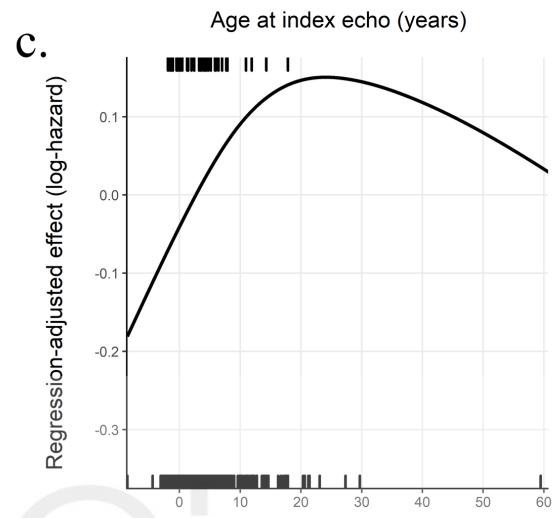
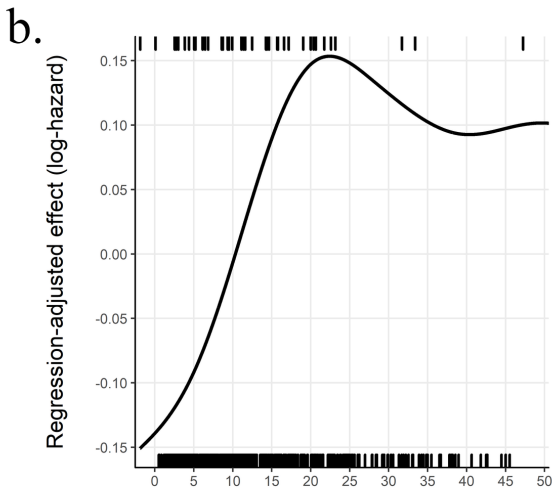
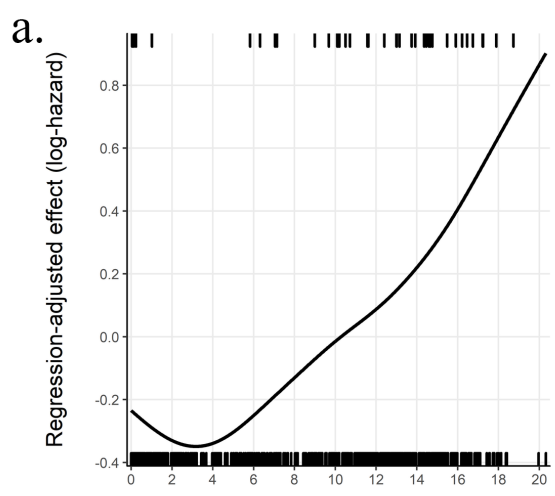
At-risk: 285 202 128 90 53 33



At-risk:

Low SCD risk:	191	162	139	123	104	90
Medium SCD risk:	190	161	140	116	97	78
High SCD risk:	191	138	106	78	64	49





At-risk:

Low SCD risk:	191	160	137	122	107	89
Medium SCD risk:	190	159	135	116	92	74
High SCD risk:	191	142	113	79	66	54

