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FASTTRACK CLINICAL RESEARCH

A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)

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Aims Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death (SCD) in young adults. Current risk algorithms provide only a crude estimate of risk and fail to account for the different effect size of individual risk factors. The aim of this study was to develop and validate a new SCD risk prediction model that provides individualized risk estimates.

Methods and results The prognostic model was derived from a retrospective, multi-centre longitudinal cohort study. The model was developed from the entire data set using the Cox proportional hazards model and internally validated using bootstrapping. The cohort consisted of 3675 consecutive patients from six centres. During a follow-up period of 24 313 patient-years (median 5.7 years), 198 patients (5%) died suddenly or had an appropriate implantable cardioverter defibrillator (ICD) shock. Of eight pre-specified predictors, age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope were associated with SCD/appropriate ICD shock at the 15% significance level. These predictors were included in the final model to estimate individual probabilities of SCD at 5 years. The calibration slope was 0.91 (95% CI: 0.74, 1.08), C-index was 0.70 (95% CI: 0.68, 0.72), and D-statistic was 1.07 (95% CI: 0.81, 1.32). For every 16 ICDs implanted in patients with $\geq$4% 5-year SCD risk, potentially 1 patient will be saved from SCD at 5 years. A second model with the data set split into independent development and validation cohorts had very similar estimates of coefficients and performance when externally validated.

Conclusion This is the first validated SCD risk prediction model for patients with HCM and provides accurate individualized estimates for the probability of SCD using readily collected clinical parameters.

Keywords Hypertrophic cardiomyopathy • Sudden cardiac death • Implantable cardioverter defibrillator • Risk prediction model

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited heart muscle disorder and a leading cause of sudden cardiac death (SCD) in young adults.[1,2] Patients at high risk of SCD need to be identified so they can be offered lifesaving treatment with an implantable cardioverter defibrillator (ICD). Contemporary guidelines recommend that the sudden death risk is assessed by evaluating clinical

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parameters that reflect the severity of the underlying myocardial disease. The presence or absence of these risk factors is then used to guide clinical decision-making with respect to prophylactic ICD implantation.[1,2] Although observational cohort studies show that this approach identifies patients with the greatest risk of SCD, validation of current algorithms suggests that they overestimate risk, resulting in inappropriate prophylactic ICD implantation in a substantial number of patients.[3] The aim of this study was to derive and validate a new sudden death risk model that can be used to generate individualized risk estimates for SCD and improve the targeting of ICD therapy in patients with HCM.

Methods

Study design and overview

The prognostic model was derived using data from a retrospective, multicentre longitudinal cohort study. The model presented in this article was developed using the entire data set, using the Cox proportional hazards model, and internally validated using bootstrapping. A secondary model with external validation was developed *de novo* using a similar modelling strategy with independent development and validation cohorts.

The study conforms to the principles of the Helsinki declaration. The sponsors of this study did not have a role in study design, data collection, analysis, and interpretation. C.O'M., R.O., F.J., and P.E. had access to all data and final responsibility to submit the article. The authors from each participating centre guarantee the integrity of data from their institution. All investigators have agreed to the article as written.

Study population and participating centres

The study cohort consisted of all consecutively evaluated patients with HCM, followed up at six participating European centres: (i) The Heart Hospital, London, UK, (ii) A Coruña University Hospital, A Coruña, Spain, (iii) Unit of Inherited Cardiovascular diseases, 1st Department of Cardiology, University of Athens, Athens, Greece, (iv) Institute of Cardiology, University of Bologna, Bologna, Italy, (v) University Hospital Virgen de la Arrixaca, Murcia, Spain, and (vi) Monaldi Hospital, Second University of Naples, Naples, Italy. Patients from this study cohort are reported in other recently published studies.[3–12]

Only adult patients ($\geq$16 years of age) with no prior ventricular fibrillation or sustained ventricular tachycardia were studied. Hypertrophic cardiomyopathy was defined as a maximum left ventricular wall thickness $\geq$15 mm unexplained by abnormal loading conditions[13] or in accordance with published criteria for the diagnosis of disease in relatives of patients with unequivocal disease.[14] Patients with known metabolic diseases (e.g. Anderson-Fabry disease) or syndromic causes of HCM (e.g. Noonan syndrome) were excluded from the study.

Patient assessment and data collection

All patients had planned clinical reviews every 6–12 months or earlier if there was a change in symptoms. Patients underwent clinical assessment, pedigree analysis, physical examination, electrocardiography (resting and ambulatory), and transthoracic echocardiography. Left ventricular outflow tract gradients were assessed at rest and on Valsalva. Data were independently collected at each participating centre using uniform methodology.

Clinical outcomes

The cause of death was ascertained by experienced cardiologists at each centre using hospital and primary health care records, death certificates, post-mortem reports, and interviews with witnesses (relatives and physicians). Deaths were assessed without knowledge of the candidate predictor variables. The primary endpoint was SCD or an equivalent event. Sudden cardiac death was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1 h of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms.[15] Aborted SCD during follow-up and appropriate ICD shock therapy were considered equivalent to SCD.[16–21] Implantable cardioverter defibrillator shocks were considered appropriate if the treated tachyarrhythmia was ventricular in origin in an identical manner to previous studies.[16–21] All ICDs had the capacity to store intracardiac electrograms.

Selection of predictor variables and coding

Risk factors of SCD which were previously examined in multiple survival studies were considered as candidate predictor variables following a review of the literature completed in January 2010.[22] Supplementary material online, *Table S1* summarizes the predictor selection algorithm, the relevant studies, and lists the candidate predictor variables. Briefly, clinical parameters were included as pre-specified predictor variables only when independently associated with SCD in at least one published multivariable survival analysis, and were uniformly defined and collected in all participating centres. The pre-specified predictors, their definitions, and coding are summarized in *Table 1*.[15,17,18,20,21,23–31] Even though both left atrial (LA) size and atrial fibrillation (AF) are associated with SCD,[31,32] only the former was included as a pre-specified predictor since LA enlargement predisposes to AF[33,34] and contained less missing data. Left ventricular end-diastolic dimension[24] was incorporated into fractional shortening to address the increasing concern of the risk of SCD in HCM patients with impaired cardiac function.[2] Echocardiographically derived ejection fraction and abnormal blood pressure response to exercise were not selected as pre-specified predictors since they have not been independently associated with SCD in any multivariable survival analyses.[15,17,21,29,30]

Sample size

To ensure that the regression coefficients of the model were estimated with adequate precision, a minimum of 10 SCD/SCD equivalent events were required per coefficient estimated by the model.[35] The 198 SCD/SCD equivalent endpoints observed in this cohort allow the estimation of 19 regression coefficients, and were sufficient to develop the model using the 8 pre-specified candidate predictors, perform sensitivity analyses, and develop a model based only on patients with complete data.

General statistical methods

All statistical analyses were carried out using STATA (version 12). Variables are expressed as mean $\pm$ standard deviation (SD), median and interquartile range (IQR) or counts and percentages as appropriate. The follow-up time for each patient was calculated from the date of their first evaluation to the date of reaching the study endpoint, or death from another cause, or to the date of their most recent evaluation. The annual event rate was calculated by dividing the number of patients reaching the endpoint by the total follow-up period for that endpoint. The cumulative probability for the occurrence of an outcome was estimated using the Kaplan–Meier method.

Missing data

To determine the degree of bias due to missing data, the characteristics of patients with missing information were compared with those with complete information. Logistic regression was used to identify the predictors of missingness. Data were assumed to be missing at random, and values for the missing predictors were imputed using multiple imputation

Table 1 Pre-specified predictor variables assessed at baseline evaluation

Predictor variable	Definition	Coding
Age	Age at evaluation.[31]	Continuous, years
Family history of SCD	History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post- or ante-mortem diagnosis).[20,23,29,30]	Binary (yes = 1/ no = 0)
Maximal wall thickness	The greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles, and apex using parasternal short-axis plane using 2-D echocardiography at time of evaluation[15,17,21,24,25,27]	Continuous, mm
Fractional shortening	(LV end-diastolic dimension-LV end-systolic dimension)/ LV end-diastolic dimension measured by M-Mode or 2D echocardiography at time of evaluation[24]	Continuous, %
Left atrial diameter	Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation[31]	Continuous, mm
Maximal left ventricular outflow tract gradients	The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three- and five-chamber views. Peak outflow tract gradients were determined using the modified Bernouilli equation: Gradient = $4V^2$, where V is the peak aortic outflow velocity[18,20,23,28,29]	Continuous, mmHg
Non-sustained ventricular tachycardia	≥3 consecutive ventricular beats at a rate of ≥120 bpm and <30 s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.[17,20,29,30]	Binary (yes = 1/ no = 0)
Unexplained syncope	History of unexplained syncope at or prior to evaluation.[20,21,26,29,31]	Binary (yes = 1/ no = 0)

techniques based on chained equations.[36] All predictors of missingness were included in the multiple imputation model, together with the outcome, all pre-specified predictors of the risk model, and the estimate of the cumulative hazard function.[37] A total of 25 imputed data sets were generated and the estimates were combined using Rubin's rules.[38] Patients with >50% missing predictors were excluded from model development.

Model development

Univariable Cox regression models were fitted for each continuous predictor to test the assumption of linearity with the outcome. To develop the final risk model, multivariable Cox regression models were fitted with all predictors and quadratic terms for the continuous predictors where non-linearity was found. The risk model was developed without centre as a predictor to allow the model to be used in other HCM populations. To avoid problems related to variable selection when the data are not very large, a 15% significance level was used in the backward elimination procedure to select the predictors for the final risk model.[39] The proportional hazards assumption required by the Cox model was investigated using Schoenfeld residuals.[40] The risk model presented in this article was developed using the entire cohort, rather than splitting it into smaller development and validation data sets, making efficient use of the data.[41]

Model validation

Bootstrapping was used to evaluate the performance of the model since this is the most efficient validation procedure as all aspects of the model development, including variable selection are validated.[41] For this purpose, 200 bootstrap samples were generated.

The calibration slope was used to assess the degree of agreement between the observed and predicted hazards of SCD.[42] A value close to 1 suggests good overall agreement. Graphical comparisons of the observed and predicted SCD at 5 years by risk groups (group cut-offs: 0–2, 2–4, 4–6, and >6% 5-year risk of SCD) were performed. The C-index (C-uno) and D-statistic were used to measure how well the model discriminated between patients with high and low risk of SCD.[43,44] A value of 0.5 for C-index indicates no discrimination and a value equal to 1 indicates perfect discrimination. The D-statistic quantifies the observed separation between subjects with low and high predicted risks as predicted by the model and can be interpreted as the log hazard ratio for having SCD between the low and high risk groups of patients. A model with no discriminatory ability will produce a value of 0 for D-statistic, with increasing values indicating greater separation.

Model presentation

The probability of SCD at 5 years for an individual patient can be calculated using the following equation, derived from the Cox proportional hazards model:

$$\hat{P}_{\text{SCD at 5 years}} = 1 - S_0(t)^{\exp(\text{Prognostic Index})},$$

where $S_0(t)$ is the average survival probability at time t (i.e. at 5 years), and the prognostic index is the sum of the products of the predictors and their coefficients.

Secondary model development with external validation

For model development with external validation, the cohort was divided into separate development and validation cohorts. The development cohort consisted of all patients from five of the six participating centres: A Coruña University Hospital, 1st Department of Cardiology of University of Athens, University of Bologna, University Hospital Virgen de la Arrixaca, and Monaldi Hospital ($n = 2082$ with 109 SCD endpoints). The model was fitted in the development cohort using penalized Ridge Cox regression which adjusts the coefficients for model overfitting when the number of events is small.[39] The model derived from the development cohort was then externally validated using The Heart Hospital patients ($n = 1593$ with 89 SCD endpoints) who were excluded from model development, and were thus independent. The same validation measures as the ones used to validate the SCD risk prediction model derived from the entire data set were used.

Sensitivity analyses

A model to adjust for centre effect was developed and validated using bootstrapping. An additional sensitivity analysis was carried out by developing a model using only patients with complete data, with and without centre. The same modelling strategy and validation measures as the ones employed to develop and validate the SCD risk prediction model on the entire data set were used.

Comparison with conventional risk factors

Clinical practice guidelines consider severe hypertrophy (maximal wall thickness $\geq$30 mm), non-sustained ventricular tachycardia (NSVT), family history of SCD, and unexplained syncope as conventional risk factors of SCD.[1,2] To compare the risk model developed in this article with contemporary clinical practice, a risk score was constructed with a value of 0 (if no conventional risk factor was present), 1 (if one conventional risk factor was present), and 2 (if $\geq$2 conventional risk factors were present). This risk score was fitted as a continuous variable using the entire data and validated using bootstrapping. The C-index and the calibration slope were calculated.

Clinical implications

In patients with all the necessary data required to calculate the 5-year SCD risk using the proposed model, the implications of ICD implantation at different thresholds were compared with the observed events at 5 years. Comparisons were carried out in three patient subgroups (0 risk factors, 1 risk factors, $\geq$2 risk factors).

Results

Baseline clinical characteristics

The study cohort consisted of 3675 patients. The baseline clinical characteristics are shown in *Table 2*. Three thousand one hundred twenty nine patients (85%) fulfilled conventional diagnostic criteria and 546 patients (15%) criteria for familial disease.[14] During follow-up, 100 (3%) patients underwent alcohol septal ablation and 174 (5%) septal myectomy (8 patients (0.2%) had both procedures). During the study period, a total of 558 (15%) patients were treated with an ICD.

SCD/SCD equivalent events during follow-up

During a follow-up period of 24 313 patient years [median 5.7 years; IQR 2.8–9.2 years; range 1 month (patient reached SCD endpoint) to 33.6 years (patient censored)], 198 patients (5%) reached the SCD endpoint with an annual rate of 0.81% (95% CI: 0.71, 0.94), and a 5-year cumulative incidence of 3.8% (95% CI: 3.1, 4.5). The study outcome consisted of 53 appropriate ICD shocks (27%), 118 SCD (60%), and 27 aborted SCD (14%). Of the 198 SCD endpoints, 33 (17%) occurred within 6 months of baseline evaluation. The follow-up characteristics by centre are summarized in *Table 2*. The clinical characteristics of patients with and without the SCD endpoint are shown in *Table 3*.

Missing data

Seven hundred ninety six patients (21.7%) had at least one predictor missing. Three patients were excluded from the analysis as they had more than 50% of predictors missing. Missing data were present in seven of the eight predictors: maximal wall thickness in 11 (0.3%) patients, fractional shortening in 286 (7.8%) patients, LA diameter in 92 (2.5%) patients, left ventricular outflow gradient in 94 (2.5%) patients, NSVT in 453 (12.3%) patients, family history of SCD in 7 (0.2%) patients, and unexplained syncope in 65 (1.8%) patients. Missingness was associated with New York Heart Association functional class III/IV, amiodarone treatment at baseline, ICD implantation during follow-up, cardiovascular deaths not secondary to SCD/heart failure/stroke, non-cardiovascular deaths, and the year of exit from the study.

Model development

The exploratory univariable analyses are shown in *Table 4*. Age, maximal LV wall thickness (mm), LA diameter (mm), maximal left ventricular outflow tract gradient (mmHg), family history of SCD, NSVT, and unexplained syncope were significantly associated with SCD at the 15% significance level. Only maximal thickness was observed to have a nonlinear association with SCD and hence a quadratic term was included for this predictor. The risk of SCD associated with LV wall thickness tended to decrease with extreme hypertrophy (as assessed by maximal wall thickness). The association of maximal wall thickness and the SCD endpoint is shown in Supplementary material online, *Table S2*. The data satisfied the assumption of proportional hazards. The estimates of the hazard ratios and the corresponding confidence intervals for the prediction model are shown in *Table 5*. The risk of SCD in 5 years for an individual HCM patient can be calculated from the following equation:

$$\hat{P}_{\text{SCD at 5 years}} = 1 - 0.998^{\exp(\text{Prognostic Index})},$$

where Prognostic Index = 0.15939858*Maximal wall thickness (mm) − 0.00294271*Maximal wall thickness^2 (mm^2) + 0.0259082*Left atrial diameter (mm) + 0.00446131*Maximal left ventricular outflow tract gradient (mmHg) + 0.4583082*Family history SCD + 0.82639195*NSVT + 0.71650361*Unexplained syncope −0.01799934*Age at clinical evaluation (years).

Model validation

Bootstrapping validation revealed a calibration slope of 0.91 (95% CI: 0.74, 1.08). *Figure 1* illustrates a good agreement between the observed and predicted risk of SCD at 5 years. The C-index was 0.70 (95% CI: 0.68, 0.72). The D-statistic was 1.07 (95% CI: 0.81, 1.32) suggesting that the hazard of SCD is 2.91 times higher in the high risk group compared with the hazard in the low risk group as predicted by the model.

Secondary model development with external validation

The estimates of hazard ratios from the secondary model developed from patients excluding the Heart Hospital were similar to those obtained using the entire data set (Supplementary material online, *Table S3*). The results from external validation were also similar to those obtained from the bootstrapped model: calibration slope: 0.95 (95% CI: 0.67, 1.24); C-index: 0.67 (95% CI: 0.64, 0.70); D-statistic: 1.14 (95% CI: 0.75, 1.53).

Table 2 Cohort characteristics

	All	The Heart Hospital, UK	A Coruña University Hospital, Spain	1St Department of Cardiology, University of Athens, Greece	Institute of Cardiology, Bologna, Italy	University Hospital Virgen de la Arrixaca, Spain	Monaldi Hospital, Italy
Baseline							
Number of patients	3675[a]	1593 (43%)	590 (16%)	474 (13%)	456 (12%)	406 (11%)	156 (4%)
Male	2349 (64%)	1,018 (64%)	364 (62%)	340 (72%)	292 (64%)	243 (60%)	92 (59%)
Age; years[b]	48 ± 17	43 ± 15	57 ± 15	47 ± 16	50 ± 17	53 ± 17	44 ± 16
NYHA III/IV	426 (12%)	136 (8.5%)	76 (13%)	77 (16%)	41 (9%)	82 (20%)	14 (9%)
Myectomy	34 (1%)	17 (1%)	6 (1%)	1 (0.2%)	5 (1%)	2 (0.5%)	3 (2%)
Alcohol septal ablation	10 (0.3%)	4 (0.3%)	2 (0.3%)	0	2 (0.4%)	2 (0.5%)	0
Amiodarone	468 (13%)	217 (14%)	79 (13%)	44 (9%)	78 (17%)	39 (10%)	11 (7%)
ICD	42 (1%)	14 (1%)	6 (1%)	1 (0.2%)	5 (1%)	8 (2%)	8 (5%)
Permanent /persistent AF	366 (10%)	98 (6%)	133 (23%)	39 (8%)	19 (4%)	65 (16%)	12 (8%)
NSVT	634 (17%)	300 (19%)	82 (14%)	56 (12%)	80 (18%)	85 (21%)	31 (20%)
LA diameter; mm[b]	44 ± 8	44 ± 8	45 ± 8	44 ± 6	46 ± 9	44 ± 8	45 ± 8
$LVOTG_{max}$; mmHg[b]	12 (5–49)	9 (5–46)	10 (7–45)	10 (4–60)	20 (15–50)	4 (4–60)	4 (4–40)
LVedd; mm	45 ± 7	44 ± 6	45 ± 6	47 ± 5	44 ± 7	44 ± 7	46 ± 7
MWT; mm[b]	20 ± 5	20 ± 6	20 ± 5	18 ± 4	20 ± 5	20 ± 5	20 ± 5
FS; %[b,c]	41 ± 9	42 ± 9	41 ± 9	41 ± 7	41 ± 11	39 ± 10	32 ± 11
FHSCD	886 (24%)	482 (30%)	42 (7%)	147 (31%)	69 (15%)	110 (27%)	36 (23%)
Unexplained syncope	507 (14%)	274 (17%)	55 (9%)	90 (19%)	11 (2%)	55 (14%)	22 (14%)
Follow-up							
Enrolment period	1972–2011	1988–2005	1983–2010	1993–2011	1972–2011	1983–2009	2001–2010
End of follow-up period	2012	2010	2011	2012	2011	2011	2011
Total patient-years	24 313.4	11 779.4	4009.3	3709.8	2955.7	1274.2	584.6
Median follow-up; years	5.7 (2.8, 9.2)	6.6 (4.2, 10.0)	6.0 (3.5, 9.2)	7.4 (4.5, 11.1)	3.4 (1.2, 8.8)	2.5 (0.8,5.4)	3.8 (1.6, 5.4)
SCD endpoints	198 (5%)	89 (6%)	20 (3%)	25 (5%)	41 (9%)	20 (5%)	3 (2%)
5-year cumulative hazard; % (95% CI)	3.8% (3.1,4.5)	3.8% (2.9,5.0)	1.6% (0.8,3.3)	3.4% (2.1,5.6)	6.1% (3.8,9.7)	5.5% (3.3,9.0)	2.0% (0.7,6.2)

Variables are expressed as mean ± standard deviation (SD), median and interquartile range (IQR) or counts and percentages as appropriate.
NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia; LA, left atrium; LVOTG, left ventricular outflow tract gradient at rest or Valsalva; LVedd, left ventricular end diastolic dimension; MWT, maximal wall thickness; FS, fractional shortening; FHSCD, family history of sudden cardiac death; SCD, sudden cardiac death.
[a]Three patients were excluded from model development because >50% of predictors were missing. One of the three excluded patients had suffered SCD/appropriate ICD shock.
[b]Range: 1%; 99% centiles: age: 16.9; 81.4 years, LA diameter: 28; 67 mm, $LVOTG_{max}$: 2; 154 mmHg, MWT: 10; 36 mm, FS: 15; 64%.
[c]207 patients (5%) with FS < 27%, 489 patients (13%) with FS>50%.

Table 3 The clinical characteristics of patients with and without the sudden cardiac death endpoint

Clinical characteristic	Patients without SCD endpoints, $n = 3477$	Patients with SCD endpoints, $n = 198$
Male	2207 (63%)	142 (72%)
Age; years	49 ± 17	43 ± 15
NYHA III/IV	395 (12%)	31 (17%)
Myectomy	202 (6%)	6 (3%)
Alcohol septal ablation	96 (3%)	4 (2%)
Amiodarone	412 (12%)	47 (23%)
Permanent /persistent AF	339 (10%)	27 (13%)
NSVT	572 (19%)	62 (31%)
LA diameter; mm	44 ± 8	46 ± 9
$LVOTG_{max}$; mmHg	11 (5–49)	18 (6–58)
LVedd; mm	45 ± 6	45 ± 8
MWT; mm	19 ± 5	22 ± 6
FS; %	41 ± 9	41 ± 10
FHSCD	813 (23%)	73 (37%)
Unexplained syncope	455 (13%)	52 (26%)

Variables are expressed as mean ± standard deviation (SD), median and interquartile range (IQR) or counts and percentages as appropriate
NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia; LA, left atrium; LVOTG, left ventricular outflow tract gradient at rest or Valsalva; LVedd, left ventricular end diastolic dimension; MWT, maximal wall thickness; FS, fractional shortening; FHSCD, family history of sudden cardiac death; SCD, sudden cardiac death.

Sensitivity analyses

The estimates of hazard ratios from the model adjusting for centre effects were similar to the developed model without centre and are shown in *Table 5*. The calibration slope for this model was 0.876 (95% CI: 0.869, 0.883), C-index was 0.69 (95%: CI 0.68, 0.71), and D-statistic was 1.115 (95% CI: 1.065, 1.164). The SCD risk models developed using only patients with complete data, with and without centre were also similar to the model developed in the primary analysis using bootstrapping (Supplementary material online, *Tables S4* and *S5*).

Comparison with conventional risk factors

The model with a continuous risk score based on the current practice of using four conventional risk factors produced a C-index of 0.54 (95% CI: 0.51, 0.56) and calibration slope of 1.02 (95% CI: 0.73, 1.30).

Clinical implications

The clinical implications of using the model were examined in 3066 patients with the necessary data to calculate the 5-year SCD risk. *Table 6* shows the simulated effect of using different thresholds of 5-year SCD risk to implant an ICD in patient subgroups defined using conventional risk factors. The 5-year SCD risk estimates that correctly identified the maximum number of SCD endpoints at 5 years and simultaneously minimized ICD implantation in patients without the SCD endpoint were ≥6% for patients with ≥2 conventional risk factors (*Figure 2A*) and ≥4% for patients with a single risk factor (*Figure 2B*). In patients with no risk factors where contemporary guidelines do not recommend primary prophylaxis ICD,[2] a ≥3% 5-year SCD risk would have resulted in ICD implantation in 8 (32%) of 25 patients with SCD endpoints and 264 (17%) patients without SCD endpoints (*Figure 2C*).

Table 4 Summary of the characteristics of patients with sudden cardiac death endpoints and univariable Cox regression models

Predictor variable	SCD group characteristics ($n = 198$)[a,b]	Hazard ratio	95% confidence interval	*P*-value
Age (years)	42.5 ± 15	0.988	0.979, 0.997	0.007
Maximal wall thickness (mm)	21.5 ± 6	1.048	1.025, 1.071	<0.001
Fractional shortening (%)	41.0 ± 10	0.992	0.977, 1.008	0.344
Left atrial diameter (mm)	46.2 ± 9	1.035	1.018, 1.052	<0.001
Left ventricular outflow gradient (mmHg)	18 (6–58)	1.005	1.001, 1.008	0.005
Family history of sudden cardiac death	73 (37%)	1.760	1.318, 2.350	<0.001
Non-sustained ventricular tachycardia	62 (31%)	2.533	1.849, 3.469	<0.001
Unexplained syncope	52 (26%)	2.326	1.693, 3.195	<0.001

Variables are expressed as mean ± standard deviation (SD), median and interquartile range (IQR) or counts and percentages as appropriate.
[a]Range of values (minimum; maximum) in SCD group: age: 16.3; 77.4 years, maximal wall thickness: 9; 37 mm, fractional shortening: 15; 62%, left atrial diameter: 28; 70 mm, maximal left ventricular outflow tract gradient: 2;190 mmHg.
[b]Missing data in SCD group: maximal wall thickness: 3%, fractional shortening: 11%, left atrial diameter: 6%, left ventricular outflow tract gradient: 3%, non-sustained ventricular tachycardia: 19%, unexplained syncope: 2%.

Table 5 Sudden cardiac death risk prediction model and sensitivity analysis for centre effect

Predictor variable	SCD risk prediction model		Sensitivity analysis: model with centre	
	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Age (years)	0.98 (0.97, 0.99)	0.001	0.98 (0.97, 0.99)	<0.001
Maximal wall thickness (mm)	1.17 (1.01, 1.37)	0.042	1.15 (0.99, 1.35)	0.069
Maximal wall thickness^2 (mm^2)	0.997 (0.99, 1.0003)	0.078	0.997 (0.99, 1.001)	0.116
Left atrial diameter (mm)	1.03 (1.01, 1.05)	0.006	1.02 (1.01, 1.04)	0.008
LV outflow gradient (mmHg)	1.004 (1.001, 1.01)	0.021	1.004 (1.0004, 1.01)	0.031
Family history SCD	1.58 (1.18, 2.13)	0.002	1.62 (1.20, 2.19)	0.002
NSVT	2.29 (1.64, 3.18)	<0.001	2.14 (1.53, 2.99)	<0.001
Unexplained syncope	2.05 (1.48, 2.82)	<0.001	2.29 (1.64, 3.20)	<0.001
Centre				
London	—		Baseline: 1 (–)	0.0015
Athens	—		0.999 (0.64, 1.57)	
Bologna	—		2.08 (1.39, 3.12)	
Coruna	—		1.08 (0.65, 1.79)	
Murcia	—		2.04 (1.22, 3.41)	
Naples	—		0.73 (0.23, 2.33)	

LV, left ventricle; NSVT, non-sustained ventricular tachycardia.

A 5-year SCD risk of ≥4% identified 60 (71%) of 84 SCD endpoints with 896 (30%) ICD implants in patients without SCD at 5 years (*Figure 2D*). For every 16 ICD implantations in patients with ≥4% 5-year SCD risk, 1 patient can potentially be saved from SCD at 5 years. Patients not reaching the SCD endpoint at 5 years ($n = 2982$) had a mean predicted 5-year SCD risk of 3.7% (IQR: 1.8–4.5%), while the corresponding figures for those reaching the SCD endpoint ($n = 84$) were 7.3% (IQR: 3.4–10%).

Discussion

This is the first validated risk prediction model for SCD in patients with HCM. The model was derived from a large, diverse, and well-characterized population of patients followed at six different European centres and provides accurate, individualized estimates for the probability of SCD using readily collected clinical parameters. The broad patient inclusion criteria of the study mean that the model can be used in the majority of adult patients with HCM, including those with mild disease identified during family screening.

Current clinical guidelines for HCM in the USA and Europe recommend SCD risk algorithms based on a simple summation of a limited number of binary clinical parameters (NSVT, severe hypertrophy, unexplained syncope, family history of SCD, and abnormal BPRE).[1,2] Even though this approach has been used in clinical practice for more than a decade, it provides only a very crude estimate of relative risk of SCD and fails to account for the different effect size of individual risk factors.[3] Moreover, some risk factors such as hypertrophy are considered as binary variables when in fact they are associated with a continuous increase in SCD risk.[25] As a result, existing algorithms have a low positive predictive accuracy for SCD that results in the unnecessary treatment of patients who are at intrinsically low risk.[3]

The usefulness of this model lies in providing accurate prognostic information that aids clinical decision making. The model achieved this by showing good agreement between the predicted and observed hazards of SCD and by demonstrating the ability to separate patients with regard to their 5-year risk of SCD.[42] The C-indices indicated that the proposed risk prediction model has superior discrimination compared with the model of conventional risk factors used in contemporary clinical practice. The sensitivity analysis demonstrated that the relationship between the predictors and SCD remains unchanged with the inclusion of centre in the model and the risk model without centre is proposed for general clinical use.

The risk prediction model has the potential to improve the management of patients with a solitary and multiple risk factors by simultaneously reducing unnecessary and potentially harmful ICD implants in patients who do not suffer SCD and correctly identifying the majority of those who suffer SCD and are most likely to benefit from an ICD. Currently, patients without conventional risk factors are reassured and reassessed and are not routinely offered ICD therapy.[1,2] However, approximately one-third of all SCD come from this subgroup of patients, and contemporary management strategies fail to address this problem. The risk prediction model may help identify a small proportion of SCD in this group which represents an improvement when compared with current clinical practice, but the performance of the model in this patient subgroup is not optimal.

The probability of SCD at 5 years is derived from a range of readily available clinical parameters, each with a unique contribution to risk. For example, consider the management of two patients with NSVT, maximal wall thickness of 23 mm, and LA diameter of 44 mm. One is aged 24 years with a resting $LVOTG_{max}$ of 64 mmHg and the other is 64 years old with an $LVOTG_{max}$ of 36 mmHg. Current guidelines treat these two patients identically as they each have a single risk factor (NSVT). By applying the clinical risk prediction model in this clinical

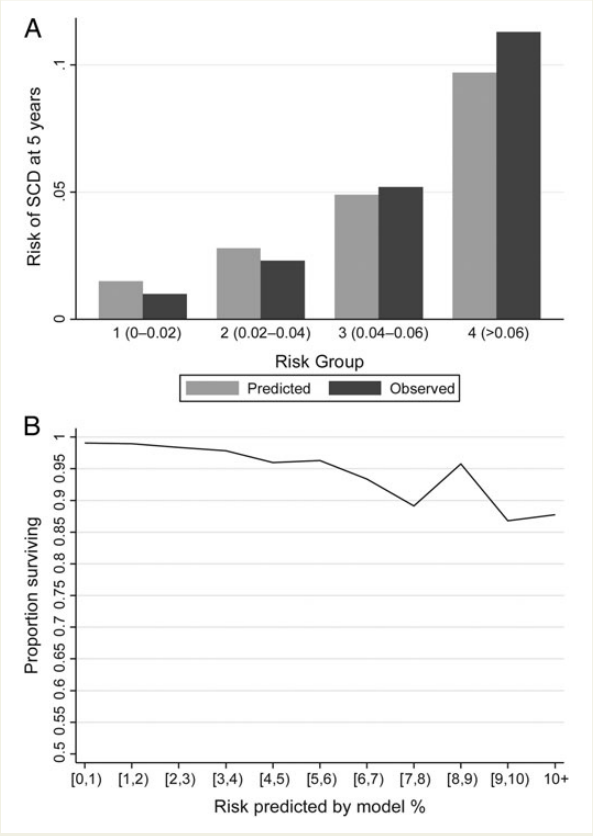

Figure 1 (*A*) Calibration by risk group. Vertical bars represent observed (black) and model-based predicted (grey) predicted probabilities of sudden cardiac death in 5 years. The four risk groups (1–4) were created using model-based predicted probabilities (0–2, 2–4, 4–6, and >6% 5-year risk of SCD).These groups are selected for the purposes of validation rather than clinical decision making. (*B*) Plot showing the proportion surviving by risk, as predicted by the model. The graph compares the risk of SCD as predicted from the model with the observed SCD endpoints at 5-years (combining 5 random imputations). The horizontal axis labels indicate the risk groups, e.g. [0–1) indicates a predicted risk of 0 to <1, [1–2) is a risk of 1 to <2, etc.

scenario, the 5-year risk of SCD is estimated at 9.7% for the first patient and at 4.3% for the latter. We envisage that an on-line risk calculator can be used to estimate the SCD risk, and this information can then be shared and discussed with patients and their families (www.HCMRisk.org).

The aim of this prediction model, like any other prognostic tool, is not to render physicians' clinical judgment obsolete, but rather to complement clinical reasoning by providing objective individualized prognostic information.[45,46] Guidelines recommend ICD therapy for the primary prevention of SCD in high risk patients,[1,2] but there is no international consensus on the absolute SCD risk that justifies ICD therapy. The intention of the proposed SCD risk model is not to categorize patients into simplistic high or low risk groups with predefined therapeutic strategies, but to treat SCD risk as a continuum, interpreted within each patient's clinical context. So while a 5-year SCD risk of ≥4% identified 71% of patients that had a SCD endpoint, this level of risk might have different implications in an otherwise well 20 year old compared to a 70-year-old patient with significant co-morbidity. When deciding on device treatment, physicians and patients have to balance the benefits of protection from SCD against the potential hazards of therapy. Approximately one-third of ICD recipients experience implant complications or inappropriate shocks after 5 years, and while the majority of ICD-related adverse events are not life threatening, they often require hospitalization and additional invasive procedures.[10] In addition, the impact of ICD therapy on employment, driving, and recreational activities has to be considered. Ultimately, the decision on treatment rests on the relative weights of the risks and benefits of ICD therapy in individual patients.[42]

Future development of the model

Prognosis is the outcome of the interaction of host, disease, and environmental factors which can be considered as predictors in prognostic models.[42,47] The candidate predictors consisted primarily of disease factors that reflect the severity of the cardiac phenotype. Of the potential predictors relating to the host, only age was included on the basis of previously published studies. When updating the model, other factors, such as sex and ethnic background as well as environmental parameters such as social deprivation and access to health care should be investigated to improve the prognostic performance of the model. These factors may be responsible for the observed centre effect in our study. The incremental predictive value of genetic information and late gadolinium enhancement imaging can also be examined in future iterations of the model. The ultimate test of the usefulness of a prediction model is an impact study that determines whether the application of the model in routine clinical practice improves decision making, patient outcomes, and cost effectiveness.[45]

Limitations

No risk stratification strategy will ever be able to predict SCD with absolute certainty and the risk prediction model should be used by physicians experienced in the management of the condition. The model should be used only in patients with similar characteristics to the study cohort. The model is not validated in paediatric patients (<16 years), elite athletes, or in individuals with metabolic diseases (e.g. Anderson-Fabry disease) and syndromes (e.g. Noonan syndrome). Patients with a previous history of aborted SCD or sustained ventricular arrhythmia were specifically excluded from the cohort and should continue to be treated with an ICD for secondary prevention. The model does not account for patients with purely exercise induced left ventricular outflow tract obstruction[48] or for the effect of myectomy or alcohol septal ablation and thus should be used cautiously in such patients. Patients with drug refractory symptomatic left ventricular outflow tract should be considered for septal reduction therapy, irrespective of their risk of SCD. On the other hand, asymptomatic patients with left ventricular outflow tract obstruction should be treated conservatively and the severity of obstruction should be used in risk stratification. In patients with exercise induced ventricular arrhythmias,[20] strong consideration of ICD implantation should be considered. The effect of amiodarone and β-blocker treatment on the risk of SCD was not examined.

The SCD risk tended to fall in patients with extreme hypertrophy. Patients with a maximal wall thickness≥ 35 mm had a very low SCD

Table 6 The simulated effect of using different thresholds of 5-year sudden cardiac death risk to implant an implantable cardioverter defibrillator in patient groups defined using conventional risk factors as recommended in current treatment guidelines

Patient groups defined using four conventional risk factors	Estimate for 5-year SCD risk used to implant ICD (%)	Patients reaching SCD endpoint[a]		Patients without SCD endpoint[b]	
		ICD implant	No ICD Implant	No ICD implant	ICD implant
Two or more conventional risk factors: 412 patients with 32 SCD endpoints at 5 years	≥3	32 (100%)	0	9 (2%)	371 (98%)
	≥4	32 (100%)	0	32 (8%)	348 (92%)
	≥5	32 (100%)	0	69 (18%)	311 (82%)
	≥6	31 (97%)	1 (3%)	131 (34%)	249 (66%)
Single conventional risk factor: 1074 patients with 27 SCD-endpoints at 5 years	≥3	27 (100%)	0	338 (32%)	709 (68%)
	≥4	24 (89%)	3 (11%)	580 (66%)	467 (44%)
	≥5	18 (67%)	9 (33%)	754 (62%)	293 (28%)
	≥6	12 (44%)	15 (56%)	877 (84%)	170 (16%)
No conventional risk factors: 1580 patients with 25 SCD endpoints at 5 years	≥2	18 (72%)	7 (28%)	822 (53%)	733 (47%)
	≥3	8 (32%)	17 (68%)	1291 (83%)	264 (17%)
	≥4	4 (16%)	21 (84%)	1474 (95%)	81 (5%)
	≥5	0	25 (100%)	1531 (99%)	24 (1%)
All patients: 3066 patients with 84 SCD endpoints at 5 years[c]	≥3	67 (80%)	17 (20%)	1638 (55%)	1344 (45%)
	≥4	60 (71%)	24 (29%)	2086 (70%)	896 (30%)
	≥5	50 (60%)	34 (40%)	2354 (79%)	628 (21%)
	≥6	43 (51%)	41 (49%)	2556 (86%)	426 (14%)

[a]Denominator for %= number of SCD endpoints.
[b]Denominator for %= number of patients without SCD endpoints.
[c]During the study period of 1972–2011, of the 3066 patients with the necessary data required to calculate the 5-year SCD risk, 49% with ≥2 risk factors, 19% with a single risk factor, and 5% with no conventional risk factors had an ICD.

rate (Supplementary material online, *Table S2*) which is reflected in the nonlinear relation between maximal wall thickness and 5-year SCD risk. This subgroup was also small in size, and pending further analysis, the model should also be used cautiously in patients with maximal wall thickness ≥ 35 mm.

This work is not an epidemiological study exploring new associations with SCD. Instead, previously described associations were used to develop a prognostic model. Predictors were only included if shown to be independently associated with SCD in published multivariable survival analyses. This strategy achieved a high event-to-predictor ratio which improves the generalizability and accuracy of predictions.

Although prospective cohort studies are desirable,[46] the low rate of SCD in HCM made a prospective design impractical. All participating centres assess HCM patients in an almost identical manner, which allowed the use of retrospectively collected data from all sites. The prediction model will be further improved through the incorporation of additional cohorts, thus increasing the number of events that will reduce model optimism.[42]

Conclusions

The risk prediction model proposed in this study provides accurate prognostic information regarding SCD in HCM. The model provides the basis for a rational and informed approach to treatment that empowers patients by helping them to understand the relative merits of prophylactic therapies including implantable cardioverter defibrillators.

Hypertrophic Cardiomyopathy Outcomes Investigators (www.HCMRisk.org)

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Authors' contributions

C.O'M designed the study, collected and interpreted the data, carried out the descriptive statistical analysis, and wrote the article. P.M.E. designed the study, interpreted the data, and wrote the article. R.Z.O. was involved in study design, led the statistical aspects of the risk modelling and wrote the article. F.J. carried out the statistical analysis. Dr Rahman evaluated some of the measures used for model validation as part of his PhD thesis with Prof Omar. M.P. carried out the statistical analysis in relation to the external validation of the model. LM., A.A., E.B., J.R.G., G.L., and C.R. collected and interpreted

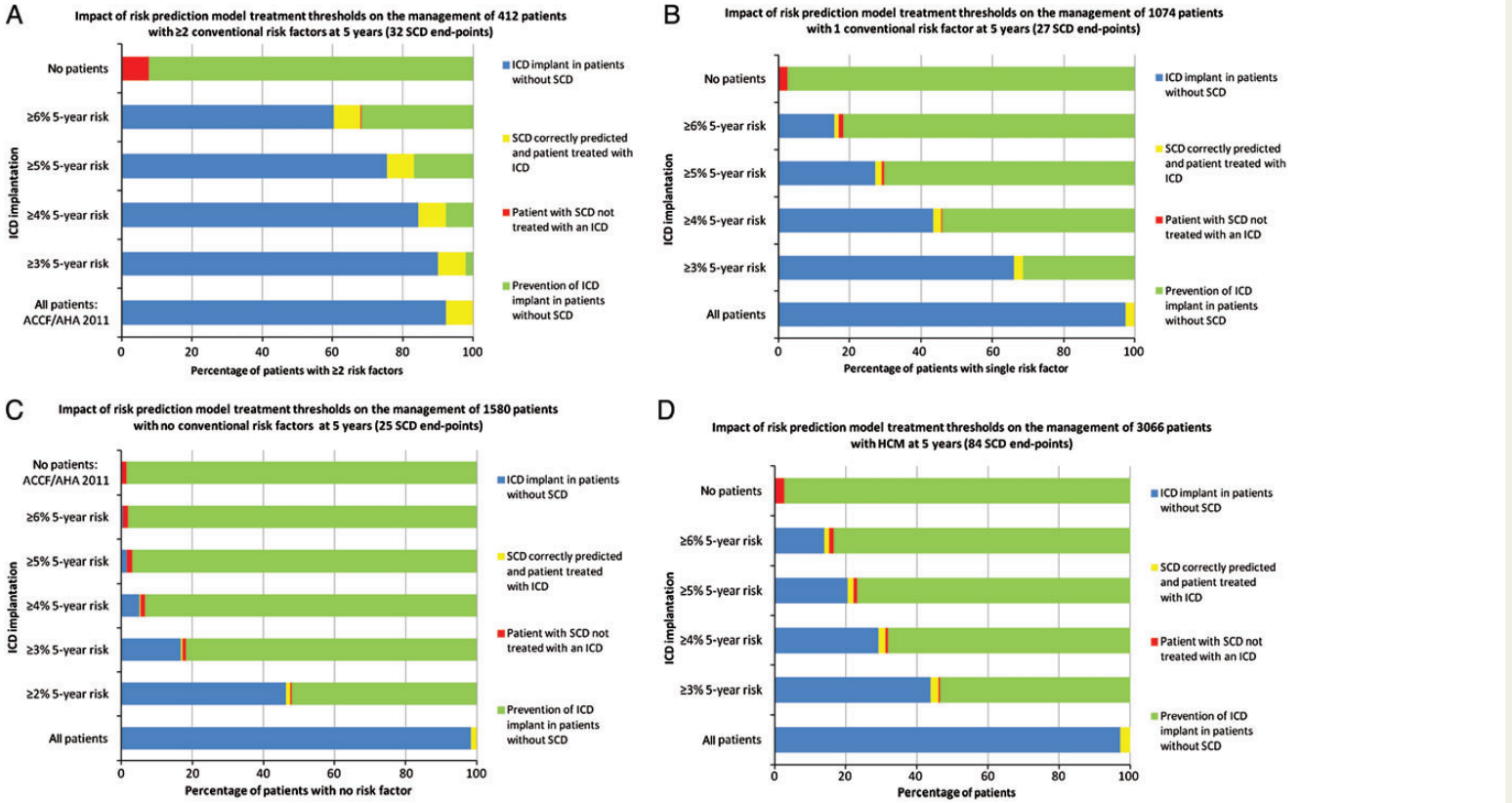

Figure 2 The impact of the risk prediction model on clinical decision making. Conventional risk factors (wall thickness ≥30 mm, NSVT, family history of SCD and unexplained syncope) were used to classify patients in those with multiple (*A*), single (*B*), no risk factors (*C*). Each figure shows the implications of implanting an ICD in all (bottom bar) or none of the patients (top bar), while the rest of the bars show the impact of using a threshold of ≥3, ≥4, ≥5, ≥6 5-year SCD risk to implant an ICD. The impact on the whole cohort is shown in (*D*). The raw data are shown in *Table 6*. Only patients with all data necessary for the 5-year SCD risk calculation were included ($n = 3066$).

the data and critically reviewed the manuscript. Ortiz-Genga, Fernandez, Vlagouli, Sandoval, Pacileo, Pantazis, Tome-Esteban, Dickie, Lambiase, Stefanadis, Coccolo, and Masarone were involved in data collection and interpretation. W.J.M. was involved in the drafting of the article and revising it critically for important intellectual content.

Ethics approval

Patients at A Coruña University Hospital (Spain), Unit of Inherited Cardiovascular diseases at the 1st Department of Cardiology (Athens), University Hospital Virgen de la Arrixaca (Spain), and Monaldi Hospital (Italy) provided written informed consent. The ethics committees at Heart Hospital (UK), and Institute of Cardiology at the University of Bologna (Italy) were informed, but approval was not required under local research governance arrangements.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: L.M. is shareholder in Health in Code SL. All other authors have no conflicts of interest to declare.

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