A NOVEL CLINICAL RISK PREDICTION MODEL FOR SUDDEN CARDIAC DEATH IN HYPERTROPHIC CARDIOMYOPATHY (HCM risk)

SUPPLEMENTARY DATA

SUPPLEMENTARY TABLE 1: Summary of candidate predictors following a review of the literature.\*

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| --- | --- | --- |
| ***Candidate predictor*** | **Total number of studies using multivariable survival analysis with SCD as an end-point** | **Number of studies showing significant independent association with SCD in a multivariable survival analysis** |
| *Age* | 71-7 | 17 |
| *Sex* | 61,2,4-6,8 | 0 |
| *Non-sustained ventricular tachycardia on Holter‡* | 111,3,6,9-16 | 36,14,15 |
| *Severe hypertrophy on echocardiography* | 151,3-7,10-12,14-19 | 55,10,11,16,19 |
| Abnormal blood pressure response to exercise*†* | 510,11,14-16 | 0 |
| *Family history of SCD* | 111,3,6,10-12,14-16,19,20 | 36,14,15 |
| *Unexplained syncope* | 111,3,6,7,10-12,14-16,20 | 53,7,14-16 |
| *Left ventricular outflow tract obstruction* | 91,3,4,6,8,14-16,19 | 51,4,8,14,15 |
| *Atrial fibrillation* | 51-5 | 12 |
| *Left atrial size on echocardiography* | 41,5,7,19 | 17 |
| New York Heart Association class *III/IV* | 61,3-5,19 | 0 |
| *Left ventricular end diastolic dimension on echocardiography* | 31,5,19 | 119 |

\*The selection of predictors involved the following algorithm (selection completed in January 2010):

1. Medline search: (MeSH terms: [“Cardiomyopathy, Hypertrophic” OR “Cardiomyopathy, Hypertrophic, Familial”] AND [“Death, Sudden, Cardiac” OR "Mortality" OR "Death”]. The initial search was supplemented with manual searches. The studies were restricted to those in published in English, with emphasis to studies which employed survival analysis in unselected HCM cohorts, with SCD as an end-point.
2. Risk factors examined in 2 or more survival studies using SCD as an end-point were considered as candidate predictors
3. Risk factors that were independently associated with SCD in a multivariable analysis were included as the final pre-specified predictors.

† Abnormal blood pressure response to exercise was defined as the failure to increase systolic blood pressure from baseline and/or a drop in systolic blood pressure from baseline or the maximum systolic blood pressure recorded during exercise in patients ≤40 years.

‡ All studies used Holter monitoring with a minimum monitoring duration of 24 hours. All studies showing a significant association with SCD defined NSVT as ≥3 consecutive ventricular beats at a rate of ≥120 bpm and <30s in duration. The rate or frequency of NSVT has not been associated with SCD.11,21

**SUPPLEMENTARY TABLE 2: The risk of SCD associated with maximal wall thickness (Cox regression model)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Patient group according to maximal wall thickness\**** | **Number of patients** | **SCD end-points in group** | **HR** | **95% CI** | **P** |
| ***≤14mm*** | 546 | 22 (4%) | Baseline group | | |
| ***15-19mm*** | 1427 | 53 (4%) | 1.01 | 0.61, 1.66 | 0.965 |
| ***20-25mm*** | 1089 | 61 (6%) | 1.44 | 0.88, 2.34 | 0.142 |
| ***25-29mm*** | 383 | 33 (9%) | 2.00 | 1.17, 3.43 | 0.012 |
| ***30-34mm*** | 169 | 23 (14%) | 3.28 | 1.82, 5.89 | <0.0001 |
| ***≥35mm†*** | 48 | 1 (2%) | 0.37 | 0.49, 2.71 | 0.325 |

**\***13 patients had missing maximal wall thickness

† Median follow-up duration for patients with MWT ≥35mm: 9.6 years (IQR 5.8, 13.4) versus 5.6 years (2.8, 9.2) for the rest of the cohort

**SUPPLEMENTARY TABLE 3: SCD risk model developed with independent development and validation cohorts (secondary model)**

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| --- | --- | --- | --- |
| **Penalized Cox regression** | | | |
| **Predictor variable** | **Hazard ratio** | **95% Confidence intervals** | |
| ***Age (years)*** | 0.98 | 0.97 | 0.99 |
| ***Maximal wall thickness (mm)*** | 1.03 | 0.96 | 1.12 |
| ***Maximal wall thickness2(mm2)*** | 0.999 | 0.998 | 1.001 |
| ***Left atrial diameter (mm)*** | 1.03 | 1.00 | 1.05 |
| ***LV outflow gradient (mmHg)*** | 1.00 | 1.00 | 1.01 |
| ***Family history of SCD*** | 1.47 | 0.96 | 2.27 |
| ***Non-sustained ventricular tachycardia*** | 2.37 | 1.45 | 3.86 |
| ***Unexplained syncope*** | 2.33 | 1.42 | 3.81 |

A secondary analysis was carried out where the risk model was developed on data from all centres excluding The Heart Hospital (n=2082) using penalised Ridge regression. This risk model was then externally validated in The Heart Hospital cohort (n=1593) as reported in the manuscript.

**SUPPLEMENTARY TALE 4: Sensitivity analysis of SCD risk prediction model using a complete case model without centre.**

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| --- | --- | --- | --- | --- |
| ***Predictor variable*** | **SCD risk prediction model** | | **Complete case model** | |
| **Hazard Ratio**  **(95% Confidence Interval)** | **p** | **Hazard Ratio**  **(95% Confidence Interval)** | **p** |
| *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 | 1.21 (1.005, 1.47) | 0.045 |
| *Maximal wall thickness2 (mm2)* | 0.997 (0.99, 1.0003) | 0.078 | 0.997 (0.99, 1.0007) | 0.117 |
| *Fractional shortening (%)* | - | - | 0.99 (0.97, 1.004) | 0.125 |
| *Left atrial diameter (mm)* | 1.03 (1.01, 1.05) | 0.006 | 1.03 (1.01, 1.05) | 0.004 |
| *LV outflow gradient (mmHg)* | 1.004 (1.001, 1.01) | 0.021 | 1.004 (1.0002, 1.01) | 0.041 |
| *Family History SCD* | 1.58 (1.18, 2.13) | 0.002 | 1.44 (1.01, 2.05) | 0.043 |
| *NSVT* | 2.29 (1.64, 3.18) | <0.001 | 2.47 (1.74, 3.51) | <0.001 |
| *Unexplained syncope* | 2.05 (1.48, 2.82) | <0.001 | 2.13 (1.46, 3.08) | <0.001 |

**SUPPLEMENTARY TABLE 5: Sensitivity analysis of SCD risk prediction model in a complete case model with centre.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Predictor variable*** | | **Sensitivity analysis (model with centre):**  **SCD risk prediction model** | | **Sensitivity analysis (model with centre):**  **Complete case model** | |
| **Hazard Ratio**  **(95% Confidence Interval)** | **p** | **Hazard Ratio**  **(95% Confidence Interval)** | **p** |
| *Age (years)* | | 0.98 (0.97, 0.99) | <0.001 | 0.981 (0.97, 0.99) | 0.004 |
| *Maximal wall thickness (mm)* | | 1.15 (0.99, 1.35) | 0.069 | 1.205 (0.996, 1.46) | 0.056 |
| *Maximal wall thickness2 (mm2)* | | 0.997 (0.99, 1.001) | 0.116 | 0.997 (0.99, 1.001) | 0.146 |
| *Fractional shortening (%)* | | - | - | 0.986 (0.97, 1.005) | 0.146 |
| *Left atrial diameter (mm)* | | 1.02 (1.01, 1.04) | 0.008 | 1.031 (1.01, 1.05) | 0.005 |
| *LV outflow gradient (mmHg)* | | 1.004 (1.0004, 1.01) | 0.031 | 1.004 (0.9998, 1.01) | 0.059 |
| *Family History SCD* | | 1.62 (1.20, 2.19) | 0.002 | 1.414 (0.99, 2.02) | 0.058 |
| *NSVT* | | 2.14 (1.53, 2.99) | <0.001 | 2.398 (1.68, 3.41) | <0.001 |
| *Unexplained syncope* | | 2.29 (1.64, 3.20) | <0.001 | 2.220 (1.51, 3.26) | <0.001 |
| CENTRE | London | Baseline: 1 (-) | 0.0015 | Baseline: 1 (-) | 0.3919 |
| Athens | 0.999 (0.64, 1.57) | 1.108 (0.69, 1.77) |
| Bologna | 2.08 (1.39, 3.12) | 1.589 (0.96, 2.63) |
| Coruna | 1.08 (0.65, 1.79) | 0.763 (0.41, 1.42) |
| Murcia | 2.04 (1.22, 3.41) | 0.881 (0.398, 1.95) |
| Naples | 0.73 (0.23, 2.33) | 1.150 (0.28, 4.89) |

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