Validation of the 2014 ESC Guidelines Risk Prediction Model for the Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Running title: Vriesendorp et al - Validation of the new SCD risk prediction model

Pieter A. Vriesendorp, MD1; Arend F.L. Schinkel, MD, PhD1; Max Liebregts, MD2; Dominic A.M.J. Theuns, PhD1; Johan van Cleemput, MD, PhD3; Folkert J. ten Cate, MD, PhD1; Rik Willems, MD, PhD2; Michelle Michels, MD, PhD1

1Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam; 2Department of Cardiology, St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands; 3Department of Cardiovascular Diseases of the University of Leuven, Leuven, Belgium.

Correspondence:
Pieter Vriesendorp
Department of Cardiology
Thoraxcenter, Erasmus MC
's-Gravendijkwal 230
3015 CE Rotterdam
the Netherlands
Tel: +31 10 703 3986
Fax: +31 10 703 5498
E-mail: p.vriesendorp@erasmusmc.nl

Abstract:

**Background** - The recently released 2014 ESC guidelines of hypertrophic cardiomyopathy (HCM) use a new clinical risk prediction model for sudden cardiac death, based on the HCM Risk-SCD study. Our study is the first external and independent validation of this new risk prediction model.

**Methods and Results** - The study population consisted of a consecutive cohort of 706 HCM patients without prior SCD event, from 2 tertiary referral centers. The primary endpoint was a composite of SCD and appropriate ICD therapy, identical to the HCM Risk-SCD endpoint. The 5-year SCD risk was calculated using the HCM Risk-SCD formula. ROC curves and C-statistics were calculated for the 2014 ESC guidelines, and risk stratification methods of the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines. During follow-up of 7.7 ±5.3 years, SCD occurred in 42 (5.9%) of 706 patients (age 49 ±16 years, 34% female). The C-statistic of the new model was 0.69 (95% CI 0.57-0.82, p = 0.008), which performed significantly better than the conventional risk factor models based on the 2003 guidelines (C-statistic of 0.55 95% CI 0.47-0.63, p = 0.3), and 2011 guidelines (C-statistic of 0.60, 95% CI 0.50-0.70, p = 0.07).

**Conclusions** - The HCM Risk-SCD model improves the risk stratification of HCM patients for primary prevention of SCD, and calculating an individual risk estimate contributes to the clinical decision making process. Improved risk stratification is important for the decision making before ICD implantation for the primary prevention of SCD.

**Key words:** hypertrophic cardiomyopathy, risk prediction, sudden cardiac death
Introduction

Sudden cardiac death (SCD) is a relatively rare but devastating clinical event in hypertrophic cardiomyopathy (HCM) with an incidence of 0.5-1%/year in patients with HCM. High risk patients can be protected from SCD by implantable cardioverter-defibrillators (ICD), but this protection comes at a price of inappropriate shocks and device related complications.

Originally, in the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines, the identification of high-risk patients was based on five clinical characteristics: a family history of SCD in first-degree relatives < 40 years of age, maximal left ventricular wall thickness (LVWT) of >30 mm, unexplainable syncope, non-sustained ventricular tachycardia (nsVT) and abnormal blood pressure response during exercise. Although it was clear that the risk of SCD increases with increasing number of risk factors, O’Mahony et al. demonstrated that both 2003 and 2011 guidelines distinguish high and low risk patients with only limited power. Recently the HCM Outcomes Investigators presented a novel clinical risk prediction model for SCD (HCM Risk-SCD), based on a cohort of 3675 patients from six centers. This model provides an individualized 5-year risk, based on most of the aforementioned risk factors, combined with left ventricular outflow tract (LVOT) gradient, left atrial (LA) diameter, and age at evaluation. This new model was more accurate in predicting SCD compared with the conventional risk factors, and the recently released 2014 ESC guidelines incorporated the HCM Risk-SCD model to classify patients as low risk (5-year risk of SCD <4%), intermediate risk (5-year risk of SCD 4-6%) or high risk (5-year risk of SCD >6%). ICD implantation was respectively a IIB or IIA recommendation in the latter groups.

This improvement of identification of high risk patients is a promising development in the prevention of SCD in HCM, but the final model needs external validation for
generalizability. The aim of this study is to perform an external and independent validation of the novel clinical risk prediction model, and to compare it with the 2003 and 2011 guidelines.

Methods

Study design and population

An international two-center, observational cohort design was used. The study conforms to the principles of the Helsinki Declaration and local institutional review board approval was obtained.

The study population consisted of 747 adult (≥16 years of age) consecutively evaluated patients with HCM at the University Hospital Leuven, Leuven, Belgium and the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. The same inclusion and exclusion criteria as described in the HCM Risk-SCD study were used, and 41 patients with a history of SCD prior to or as first contact were excluded. Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥15 mm, assessed by echocardiography. Patients with HCM linked to Noonan’s syndrome, Fabry’s disease, mitochondrial disease or congenital heart defects were excluded. All patients with a history of cardiac arrest or sustained ventricular tachycardia were also excluded.

Outcomes and follow-up

The primary endpoint of SCD was equivalent to the endpoint used in the HCM Risk-SCD study. It was a composite endpoint and consists of (1) instantaneous and unexpected death within 1 hour of a witnessed collapse in patients who were previously in a stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; (2) successful resuscitation after cardiac arrest; and (3) appropriate ICD interventions for VF or fast VT (>200 bpm), in line with previous studies. Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from
information provided by patients themselves or their general practitioners. For primary prevention, a cut-off rate for ventricular tachycardia (VT) detection of 175–180 b.p.m. with a series of antitachycardia pacing (ATP) bursts followed by shocks was programmed. Detection for ventricular fibrillation (VF) was usually set at 220 b.p.m. with direct shock application. All ICD interventions were evaluated by an experienced electrophysiologist at each center. Follow-up extended from first evaluation up to an endpoint or the administrative censoring date, set at November 1st, 2012. If patients were lost to follow-up, the patient would be censored at last known contact date.

**Risk factors and profiles**

Risk factors for SCD were evaluated at baseline and based on the conventional risk factors and the variables described in the HCM Risk-SCD study. The following risk factors were identified: (1) age at evaluation; (2) a family history of SCD in ≥ 1 first-degree relatives < 40 years of age or in a first degree relative with confirmed HCM at any age; (3) maximal LVWT; (3) history of unexplainable syncope; (4) documented nsVT ≥ 3 beats at a rate of ≥ 120 b.p.m.; (5) maximal LVOTO gradient (either resting or provokable gradient); (6) LA diameter measured in parasternal long axis; and (7) abnormal blood pressure response during exercise was also identified (as a conventional risk factor).

The 5-year risk of SCD for individual patients were calculated using the HCM Risk-SCD formula: 

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

where \( \text{Prognostic Index} = \)

\[ 0.15939858 \times \text{maximal LVWT (mm)} - 0.00294271 \times \text{maximal LVWT}^2 (\text{mm}^2) + 0.0259082 \times \text{LA diameter (mm)} + 0.00446131 \times \text{maximal LVOT gradient (mmHg)} + 0.4583082 \times \text{Family history of SCD} + 0.82639195 \times \text{nsVT} + 0.71650361 \times \text{unexplained syncope} - 0.01799934 \times \text{age at evaluation (years)}; \]

(The ESC calculator is
available at http://www.doc2do.com/hcm/webHCM.html). Additionally, risk profiles based on 2003 ACC/ESC guideline and 2011 ACCF/AHA guideline were calculated. In the 2003 guideline, each risk factor was of equal weight and the profile was calculated as the sum of all risk factors present in the patient. The approach for the 2011 guideline was similar, except that documented nsVT and abnormal blood pressure response during exercise only were considered if at least one of the other risk factors was present.

**Statistical Analysis**

SPSS version 21 (IBM, Armonk, NY, USA), R version 3.1.1 (The R Foundation, Vienna, Austria) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables between groups Student t test or Mann-Whitney U-test were used, and to compare categorical variables the χ²-test was used. The performance of the novel risk model, and the models based on conventional risk factors, was determined by the C-statistic, which indicates how well a model discriminates here between high and low risk for SCD in HCM patients. A C-statistic of 0.5 indicates no predictive value, and 1.0 indicates perfect performance. A receiver operating characteristic (ROC) curve was constructed to visualize the model performances, by plotting the sensitivity against 1-specificity. The C-statistic was based on a Cox regression model, using R’s `survival` and `survivalROC` packages. Kaplan-meier estimates were calculated, and compared using the log-rank test. Univariable cox regression analysis was performed to identify predictors of outcome. All tests were 2-sided and a p-value <0.05 was considered statistically significant.

To deal with missing data, we used a similar approach outlined in the HCM Risk-SCD
study: missing data was identified and imputed using multiple imputation. A total of 25 imputed data sets were generated and pooled. Patients with 50% missing predictors were excluded from model development.

**Results**

**Clinical characteristics**

The final study population consisted of 706 HCM patients (age 49 ± 16, 66% male) and Table 1 lists the baseline characteristics of these patients. A baseline LVOT gradient ≥ 30 mmHg was present in 375 patients (53%). During follow-up 109 patients (15%) underwent septal ablation and 139 patients (20%) underwent surgical myectomy. Atrial fibrillation was documented in 170 patients (24%) during follow-up. A total of 524 patients (74%) were treated with at least a β-receptor antagonist or verapamil. An ICD was implanted for primary prevention in 117 patients (17%). Risk stratification was not complete in all patients: in 107 patients (15%) the exercise testing was lacking, in 116 patients (16%) the Holter-monitoring, in 52 patients (7.3%) there was LVOT gradient, and in 52 patients LA diameter was missing. No patients were excluded because of missing data. Predictors of missingness were: age at first contact, gender, and NYHA class, and date of exit of the study.

**Sudden cardiac death**

Follow-up was 7.7 ± 5.3 years (range 22.7), with a total of 5438 patient-years. During follow-up 42 patients (5.9%) reached the SCD endpoint. Of these, 4 (10%) had successful cardiac resuscitation, 16 (38%) had appropriate ICD shocks and 22 (52%) died suddenly. Patients with SCD were younger (44 vs 50 years), had increased LVWT (23 vs 20 mm) and left atrial diameter (49 vs 45 mm). Twenty patients (28%) reached the SCD endpoint in the first 5 years after initial risk stratification. Univariable Cox-regression analysis identified only left ventricular wall...
thickness as a predictor for SCD (Table 2).

**HCM Risk-SCD score and the 2003 and 2011 guidelines**

In the patients reaching the SCD endpoint, mean calculated 5-year SCD risk was 4.9% (IQR 3.8%) and these patients had a median of 1 (IQR 2) established risk factor. In patients without SCD calculated 5-year risk was 2.8% (IQR 3.0%; p = 0.002), with a median of 0 (IQR 1) established risk factors (p=0.03).

The C-statistic for the HCM Risk-SCD model was 0.69 (95% CI 0.57-0.82, p=0.008). The C-statistic was also calculated for the 2003 guidelines: 0.55 (95% CI 0.47-0.63, p=0.3); and for the 2011 guidelines: 0.60 (95% CI 0.50-0.70, p=0.07). The ROC curves are shown in Figure 1. We also examined whether using the HCM Risk-SCD score results in correct reclassification of high-risk patients. Net reclassification index (NRI) was 0.27 (95% CI -0.02 – 0.57, p=0.07) compared with 2003 guidelines and NRI was 0.16 (95% CI -0.17 – 0.45, p=0.2) compared with 2011 guidelines. A complete overview is shown in Table 3.

**Risk groups and clinical implications**

The predicted and observed risk per group are illustrated in Figure 2, SCD risk was overestimated, especially in the high risk group. Optimal sensitivity and specificity of the HCM Risk-SCD model in the original study was determined at ≥4% per 5-year, with a sensitivity and specificity of 71% and 70%. In this study a calculated 5-year SCD risk of 4% showed similar sensitivity (70%) and specificity (67%, Figure 1), and was a significant predictor for SCD (HR 4.2 95% CI 1.6-11.0, p=0.003). In contrast, the presence of ≥1 (HR 2.2 95% CI 0.9-5.3, p=0.08; 2011 guidelines) or ≥2 (HR 1.7 95% CI 0.6-4.6, p=0.3; 2003 guidelines) risk factors were not predictive of SCD. Kaplan-Meier estimates for risk of SCD are shown in Figure 3.

To prevent 1 case of SCD in 5 years, 17 ICD implantations are necessary when using the
The 2003 and 2011 guidelines\textsuperscript{3, 4} are based on the five aforementioned established risk factors to determine whether or not patients with HCM are at increased risk of SCD. O’Mahony et al. demonstrated in 2013 that both models are limited to discern high from low risk patients\textsuperscript{5}. The HCM Risk-SCD model was developed to improve the risk stratification of HCM patients. Instead of an algorithm based on the sum of the established risk factors, as those guidelines do, this model calculates individual 5-year SCD risk estimates. Our results show that, in an independent setting, the ability to predict SCD by using the HCM Risk-SCD model (C-statistic = 0.69) is improved when compared with current guidelines (C-statistic = 0.55-0.60).

The biggest changes in the HCM Risk-SCD model, compared with the risk stratification models proposed by the older guidelines are the following: (1) abnormal blood pressure response during exercise is no longer included in the risk stratification; (2) increasing age is a protective factor; (3) LVWT is no longer regarded as dichotomous, but as a continuous variable; and (4) LA diameter and LVOT gradient are added as continuous risk factors. All clinical variables are easily obtained, especially since abnormal blood pressure response during exercise is no longer a
risk factor. Although there was a univariable association between blood pressure response and SCD, it remained unclear if it was only of clinical importance in patients ≤40 years old, or how the finding was related to the increase in dynamic LVOT gradient. In the 2011 guidelines the usefulness of ICD implantation in the presence of an abnormal blood pressure response as only risk factor was deemed uncertain (Class IIb, level of evidence C), and it was excluded as potential risk factor in the HCM Risk-SCD model because it was not associated with SCD in any multivariable survival analyses. Age is considered to be protective of SCD in this model. A number of studies have demonstrated that a younger age is associated with an increased risk of SCD, and a recent study showed a very low SCD risk in patients >60 years of age.

Cardiac remodeling and SCD

Another advantage of the new model is that the effects of cardiac remodeling on SCD are now considered. HCM is not a static disease and Olivotto et al. identified 4 clinical stages of HCM and demonstrated that disease progression is associated with an increase of SCD risk: from 0.5%-1%/year in patients with classic phenotype to 10%/year in patients with overt dysfunction. This increase of risk is not considered in the conventional risk prediction models. The new HCM Risk-SCD model is partially based on factors of disease progression including maximal LVWT, LA diameter and LVOT gradient. These factors are, as mentioned above, included in the model as continuous variables, and changes herein are reflected in the SCD risk score.

ICD implantation for primary prevention of SCD

Patients that are considered at high risk for SCD should be considered for ICD implantation, after taking into account the potential complications of long-term ICD implantation. The improved discriminatory power of the HCM Risk-SCD model might imply that more patients at increased risk (both intermediate and high risk) of SCD (a 5-year risk of 4-6% and ≥6%) are
correctly identified and become eligible for ICD implantation, but also that unnecessary and potential harmful ICD implantations in patients without increased risk of SCD can be avoided. In our population, for every 17 ICD's implanted in patients with a 5-year risk of ≥ 4%, 1 patient could be saved from SCD at 5 years. This is similar with the 16 ICD implantations needed to prevent 1 SCD in the HCM Risk-SCD study, and lower than current risk stratification models. It is important to note that the calculated risk score is not a replacement of clinical judgment, but should be used as the authors state: “to complement clinical reasoning by providing objective individualized prognostic information.” This is in line with the 2011 guidelines that state: “The decision for placement of primary prevention ICD in HCM often involves a large measure of individual clinical judgment, particularly when evidence for risk is ambiguous. The potential for SCD needs to be discussed with each fully informed HCM patient and family member in the context of their concerns and anxieties and should be balanced against the risks and benefits of proposed prophylactic ICD strategy.”

Model limitations and future developments

Further development of the model will determine the role of other clinical variables. SCD in HCM is assumed to originate from the myocardial disarray and scar tissue, which is, for example, more present in patients with increased LVWT. Several studies have shown that the presence of extensive fibrosis, demonstrated by delayed gadolinium enhancement on cardiac magnetic resonance imaging, might increase the risk of SCD, but a recent meta-analysis did not show any relationship with SCD. There is a relationship however between extensive delayed enhancement and progression to heart failure. The additional value of delayed enhancement in the prediction of SCD could be assessed in a future version of the risk prediction model.
A similar approach can be used for genetics: it is not evident whether genetic information is predictive of outcome. Genotype was not predictive of appropriate ICD interventions, but patients with double or triple mutations are at increased risk of end-stage progression and ventricular arrhythmias. Current DNA sequencing is expensive and time-consuming; especially if analysis has to be continued after the first mutation has been found. With next-generation sequencing it will be possible to screen for a larger number of genes, and it will possibly lead to identification of more patients carrying mutations. It might become easier to identify patients with multiple mutations and include this information in the individual risk stratification.

In addition, specific electrocardiographical features, such as paced electrogram fractionation analysis, may provide further improvement of the risk model. Finally, it is unclear how septal reduction therapy (both surgical myectomy and septal ablation) influences the individual SCD risk, and whether or not it is suffice to calculate the new 5-year risk by using the post-procedural LVOT gradient and LVWT. Several studies demonstrated that SCD rates after myectomy are low, but the SCD risk after septal ablation is more controversial.

Study limitations

This study has several limitations. The comparison between different risk models is limited due to the small numbers of SCD events. Both participating centers are tertiary referral centers for the diagnostic and therapeutic care of HCM, and due to this selection and referral bias, the patient population might not represent the general HCM population. As rhythm documentation of the event was not available for all SCD cases, it was not possible to ascertain that all deaths were arrhythmic in nature. Also a more conservative setting would have influenced the occurrence of ICD interventions. Risk stratification was not complete in all patients: in 107
patients (15%) the exercise testing was lacking, and in 116 patients (16%) the Holter-monitoring. The same approach to missing data was used as in the HCM Risk-SCD study.  

Conclusion

The HCM Risk-SCD model improves the risk stratification of HCM patients, and calculating an individual risk estimate contributes to the clinical decision making process. Improved risk stratification is important for the decision making before ICD implantation for primary prevention of SCD.

Conflict of Interest Disclosures: Willems R. receives unconditional research funding from Boston Scientific and Medtronic Belgium, and is supported as a clinical researcher by the Fund for Scientific Research Flanders.

References:


Table 1: Clinical characteristics of 706 HCM patients

<table>
<thead>
<tr>
<th></th>
<th>All n= 706</th>
<th>Patients with SCD 42</th>
<th>Patients without SCD 664</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>242 (34)</td>
<td>10 (24)</td>
<td>232 (35)</td>
</tr>
<tr>
<td>Age, y</td>
<td>49 ± 16</td>
<td>44 ± 17</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>232 (33)</td>
<td>19 (41)</td>
<td>213 (32)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>170 (24)</td>
<td>15 (36)</td>
<td>155 (23)</td>
</tr>
<tr>
<td>Left ventricular wall thickness, mm</td>
<td>20 ± 5</td>
<td>23 ± 5</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>45 ± 8</td>
<td>49 ± 9</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Maximal LVOT gradient, mmHg</td>
<td>48 ± 44</td>
<td>48 ± 43</td>
<td>48 ± 44</td>
</tr>
<tr>
<td>Surgical myectomy</td>
<td>139 (20)</td>
<td>6 (14)</td>
<td>133 (20)</td>
</tr>
<tr>
<td>Septal ablation</td>
<td>109 (15)</td>
<td>10 (24)</td>
<td>99 (15)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>141 (20)</td>
<td>14 (33)</td>
<td>127 (19)</td>
</tr>
<tr>
<td>Syncope</td>
<td>72 (10)</td>
<td>7 (17)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Left ventricular wall thickness ≥30mm</td>
<td>46 (7)</td>
<td>8 (19)</td>
<td>38 (6)</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>157 (22)</td>
<td>16 (38)</td>
<td>141 (21)</td>
</tr>
<tr>
<td>Abnormal blood pressure during exercise</td>
<td>89 (13)</td>
<td>5 (12)</td>
<td>84 (13)</td>
</tr>
<tr>
<td>0 Risk factors</td>
<td>345 (49)</td>
<td>12 (29)</td>
<td>333 (50)</td>
</tr>
<tr>
<td>1 Risk factor</td>
<td>245 (35)</td>
<td>17 (40)</td>
<td>228 (34)</td>
</tr>
<tr>
<td>≥ 2 Risk factors</td>
<td>116 (16)</td>
<td>13 (31)</td>
<td>103 (16)</td>
</tr>
</tbody>
</table>

Data are represented as n (percentage) unless stated otherwise. LVOT: left ventricular outflow tract; SCD: sudden cardiac death.
Table 2: Univariable Cox regression model of predictors for SCD in 706 HCM patients

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.98</td>
<td>0.96-1.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Male</td>
<td>3.0</td>
<td>0.87-10.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Left ventricular wall thickness, mm</td>
<td>1.09</td>
<td>1.02-1.17</td>
<td>0.009</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>1.05</td>
<td>0.99-1.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Maximal LVOT gradient, mmHg</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.1</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>1.7</td>
<td>0.66-4.45</td>
<td>0.3</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.6</td>
<td>0.47-5.51</td>
<td>0.4</td>
</tr>
<tr>
<td>Left ventricular wall thickness ≥30mm</td>
<td>4.6</td>
<td>1.68-12.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>1.2</td>
<td>0.46-3.21</td>
<td>0.7</td>
</tr>
<tr>
<td>Abnormal blood pressure during exercise</td>
<td>0.7</td>
<td>0.17-3.13</td>
<td>0.7</td>
</tr>
</tbody>
</table>

CI: confidence interval; HCM: Hypertrophic cardiomyopathy; HR: hazard ratio; LVOT: left ventricular outflow tract; SCD: sudden cardiac death.
<table>
<thead>
<tr>
<th>Predicted risk classified downward in new model</th>
<th>Predicted risk not changed in new model</th>
<th>Predicted risk classified upward in new model</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2014 vs. 2003 guidelines model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (SCD-patients), n (%)</td>
<td>0 (0) †</td>
<td>11 (55)</td>
<td>20</td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>12 (2)*</td>
<td>540 (79)</td>
<td>686</td>
</tr>
<tr>
<td><strong>2014 vs. 2011 guidelines model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (SCD-patients), n (%)</td>
<td>2 (10) †</td>
<td>12 (60)</td>
<td>20</td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>75 (11)*</td>
<td>513 (75)</td>
<td>686</td>
</tr>
</tbody>
</table>

* indicates correct reclassifications in the new model. † indicates incorrect reclassifications in the new model. SCD = sudden cardiac death
### Table 4: ICD implantations and 5-year risk of SCD based on the HCM Risk-SCD model, and 2003 and 2011 risk prediction models

<table>
<thead>
<tr>
<th></th>
<th>Patients with SCD</th>
<th>Patients without SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 706</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>No ICD</td>
</tr>
<tr>
<td>2003 guidelines (≥2 established risk factors)</td>
<td>5 (25)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>2011 guidelines (≥1 established risk factor)</td>
<td>10 (50)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>HCM Risk-SCD score ≥4%</td>
<td>14 (70)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

Data are represented as number (percentage). HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; SCD: sudden cardiac death.

### Figure Legends:

**Figure 1:** Time-dependent receiver operating characteristic curves for the risk prediction models of the 2014 ESC guidelines (AUC=0.69), 2003 ACC/ESC guidelines (AUC=0.55), and 2011 ACCF/AHA guidelines (AUC=0.60), and the reference line (AUC=0.5).

**Figure 2:** Predicted and observed risk of SCD in the different risk groups.

**Figure 3:** Kaplan Meier estimates of SCD risk in 706 HCM patients, based on the 2003 ACC/ESC guidelines, 2011 ACCF/AHA guidelines, and HCM Risk-SCD model (SCD risk ≥4%/5-year).
The graph shows the 5-years SCD Risk (%) for different risk groups.

- **Risk group 1 (0-2%)**
  - Predicted: 0%
  - Observed: 0%

- **Risk group 2 (2-4%)**
  - Predicted: 2%
  - Observed: 2%

- **Risk group 3 (4-6%)**
  - Predicted: 4%
  - Observed: 6%

- **Risk group 4 (>6%)**
  - Predicted: 6%
  - Observed: 9%

The graph illustrates the comparison between predicted and observed SCD risk across different risk groups.