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

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Background—The recently released 2014 European Society of Cardiology guidelines of hypertrophic cardiomyopathy (HCM) use a new clinical risk prediction model for sudden cardiac death (SCD), 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 patients with HCM without prior SCD event, from 2 tertiary referral centers. The primary end point was a composite of SCD and appropriate implantable cardioverter-defibrillator therapy, identical to the HCM Risk-SCD end point. The 5-year SCD risk was calculated using the HCM Risk-SCD formula. Receiver operating characteristic curves and C-statistics were calculated for the 2014 European Society of Cardiology guidelines, and risk stratification methods of the 2003 American College of Cardiology/European Society of Cardiology guidelines and 2011 American College of Cardiology Foundation/American Heart Association guidelines. During follow-up of 7.7±5.3 years, SCD occurred in 42 (5.9%) of 706 patients (ages 49±16 years; 34% women). 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 patients with HCM 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 implantable cardioverter-defibrillator implantation for the primary prevention of SCD. (Circ Arrhythm Electrophysiol. 2015;8:829-835. DOI: 10.1161/CIRCEP.114.002553.)

Key Words: cardiomyopathy, hypertrophic death, sudden, cardiac

Sudden cardiac death (SCD) is a relatively rare but devastating clinical event in hypertrophic cardiomyopathy (HCM) with an incidence of 0.5% to 1%/y in patients with HCM.1 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.2

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Originally, in the 2003 American College of Cardiology/European Society of Cardiology (ESC) guidelines and 2011 American College of Cardiology Foundation/AHA guidelines, the identification of high-risk patients was based on 5 clinical characteristics: a family history of SCD in first-degree relatives aged <40 years, maximal left ventricular wall thickness (LVWT) of >30 mm, unexplainable syncope, non–sustained ventricular tachycardia (VT), and abnormal blood pressure response during exercise.3,4 Although it was clear that the risk of SCD increases with increasing number of risk factors, O’Mahony et al5 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 6 centers.6 This new model was more accurate in predicting SCD compared with the conventional risk factors, and the recently released 2014 ESC guidelines incorporated...
WHAT IS KNOWN

• Using classic risk factors to identify patients with HCM at high risk of SCD is limited.
• The risk prediction model in the new European guidelines (HCM Risk-SCD score) seems to improve this risk stratification.

WHAT THE STUDY ADDS

• This is the first external and independent validation of the new model.
• The HCM Risk-SCD score discriminates better between patients with high or low SCD risk than the risk stratification models proposed by earlier clinical guidelines.

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 a IIB or IIA recommendation in the latter groups, respectively.

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 aims of this study are 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 2-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 (aged ≥16 years) consecutively evaluated adults 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 before or as first contact were excluded.6 Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥15 mm, assessed by echocardiography.34 Patients with HCM linked to Noonan syndrome, Fabry disease, mitochondrial disease, or congenital heart defects were excluded. All patients with a history of cardiac arrest or sustained VT were also excluded.

Outcomes and Follow-Up

The primary end point of SCD was equivalent to the end point used in the HCM Risk-SCD study. It was a composite end point 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 ventricular fibrillation or fast VT (>200 beats per minute), in line with previous studies.63 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 cutoff rate for VT detection of 175 to 180 beats per minute with a series of antitachycardia pacing bursts followed by shocks was programmed. Detection for ventricular fibrillation was usually set at 220 beats per minute 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 end point or the administrative censoring date, set at November 1, 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 aged <40 years or in a first-degree relative with confirmed HCM at any age, (3) maximal LVWT, (4) history of unexplained syncope, (5) documented non–sustained VT ≥3 beats at a rate of ≥120 beats per minute, (6) maximal LVOT obstruction gradient (either resting or provokable gradient), (7) LA diameter measured in parasternal long axis, and (8) abnormal blood pressure response during exercise was also identified (as a conventional risk factor).

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

$\text{Risk} = \text{age} \times \text{family history of SCD} + \text{non-sustained VT} + \text{maximal LVWT}^2 \times \text{maximal LVOT diameter} \times \text{maximal LVOT gradient} \times \text{sustained VT} \times \text{unexplained syncope} \times \text{age}$. 

This is the first external and independent validation of the novel clinical risk prediction model and to compare it with the 2003 and 2011 guidelines.

Statistical Analysis

SPSS version 21 (IBM, Armonk, NY), R version 3.1.1 (The R Foundation, Vienna, Austria), and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean±SD and non-normally distributed data are expressed as median (interquartile range [IQR]). 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 patients with HCM. A C-statistic of 0.5 indicates no predictive value, and 1.0 indicates perfect performance. A receiver operating characteristic 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 survival receiver operating characteristic 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 were 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.
Table 1. Clinical Characteristics of 706 Hypertrophic Cardiomyopathy Patients

<table>
<thead>
<tr>
<th></th>
<th>All (n=706)</th>
<th>Patients With SCD (n=42)</th>
<th>Patients Without SCD (n=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, mm/Hg</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 ≥30 mm</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 indicates left ventricular outflow tract; NYHA, New York Heart Association; and SCD, sudden cardiac death.

Results

Clinical Characteristics

The final study population consisted of 706 patients with HCM (aged 49±16; 66% men) and Table 1 lists the baseline characteristics of these patients. A baseline LVOT gradient ≥30 mm/Hg 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%) the LVOT gradient, and in 52 patients LA diameter was missing. No patients were excluded because of missing data. Predictors of missing data were age at first contact, sex, and New York Heart Association class, and date of exit of the study.

Sudden Cardiac Death

Follow-up was 7.7±5.3 years (range, 22.7 years), with a total of 5438 patient-years. During follow-up, 42 patients (5.9%) reached the SCD end point. 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 versus 50 years), had increased LVWT (23 versus 20 mm) and LA diameter (49 versus 45 mm). Twenty patients (28%) reached the SCD end point in the first 5 years after initial risk stratification. Univariable Cox-regression analysis identified only LVWT as a predictor for SCD (Table 2).

HCM Risk-SCD Score and the 2003 and 2011 Guidelines

In the patients reaching the SCD end point, 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 receiver operating characteristic 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 was 0.27 (95% CI, −0.02 to 0.57; P=0.07) compared with 2003 guidelines and net reclassification index was 0.16 (95% CI, −0.17 to 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 risks 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 were determined at ≥4% per 5 years, with a sensitivity and specificity of 71% and 70%, respectively. 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 (hazard ratio, 4.2; 95% CI, 1.6–11.0; P=0.003). In contrast, the presence of ≥1 (hazard ratio, 2.2; 95% CI, 0.9–5.3; P=0.08; 2011 guidelines) or ≥2 (hazard ratio, 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 ≥4% cutoff. The 2003 guideline model requires 22 ICD implantations to prevent 1 SCD and the 2011 guideline model requires 20 ICD implantations (Table 4).

Discussion

This study is the first independent and external validation of the novel clinical risk prediction model (HCM Risk-SCD) used in the 2014 ESC guidelines. The most important finding of this study is that in an independent setting, the HCM Risk-SCD score discriminates better between patients with high or low SCD risk than the risk stratification models proposed by older clinical guidelines.

Identification of High-Risk Patients

The 2003 and 2011 guidelines are based on the 5 aforementioned established risk factors to determine whether...
patients with HCM are at increased risk of SCD. O’Mahony et al\textsuperscript{5} demonstrated in 2013 that both models are limited to discern high from low-risk patients. The HCM Risk-SCD model was developed to improve the risk stratification of patients with HCM. 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 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 because abnormal blood pressure response during exercise is no longer a risk factor. Although there was a univariable association between blood pressure response and SCD,\textsuperscript{8} it remained unclear whether it was only of clinical importance in patients aged $\leq 40$ years,\textsuperscript{7} 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),\textsuperscript{4} 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.\textsuperscript{7,9,10} Age is considered to be protective of SCD in this model. Several studies have demonstrated that a younger age is associated with an increased risk of SCD,\textsuperscript{11–13} and a recent study showed a low SCD risk in patients aged $>60$ years.\textsuperscript{14}

### 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\textsuperscript{15} identified 4 clinical stages of HCM and demonstrated that disease progression is associated with an increase of SCD risk: from 0.5% to 1%/y in patients with classic phenotype to 10%/y 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.

### Table 3. Reclassification of Predicted Risk Among Cases (Patients With SCD Event) and Controls

<table>
<thead>
<tr>
<th></th>
<th>Predicted Risk Classified in 2014</th>
<th>Predicted Risk Not Changed in 2011</th>
<th>Predicted Risk Classified in 2014</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Downward in New Model</td>
<td>Changed in New Model</td>
<td>Upward in New Model</td>
<td></td>
</tr>
<tr>
<td>Cases (SCD patients), n (%)</td>
<td>0 (0)*</td>
<td>11 (55)</td>
<td>9 (45)*</td>
<td>20</td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>12 (2)†</td>
<td>540 (79)</td>
<td>134 (20)*</td>
<td>686</td>
</tr>
<tr>
<td>Cases (SCD patients), n (%)</td>
<td>2 (10)*</td>
<td>12 (60)</td>
<td>6 (30)†</td>
<td>20</td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>75 (11)†</td>
<td>513 (75)</td>
<td>98 (14)*</td>
<td>686</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death.
*Incorrect reclassifications in the new model.
†Correct reclassifications in the new model.
ICD Implantation for Primary Prevention of SCD
Patients who 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 ICDs 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 patient with HCM 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 MRI, 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 it is sufficient to calculate the new 5-year risk using the postprocedural 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 because of the small numbers of SCD events. Both participating centers are tertiary referral centers for the diagnostic and therapeutic care of HCM, and because of 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.

**Conclusions**

The HCM Risk-SCD model improves the risk stratification of patients with HCM 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.

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**Disclosures**

None.

**References**


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