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ORIGINAL RESEARCH ARTICLE

International External Validation Study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM)

Editorial, see p 1024

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BACKGROUND: Identification of people with hypertrophic cardiomyopathy (HCM) who are at risk of sudden cardiac death (SCD) and require a prophylactic implantable cardioverter defibrillator is challenging. In 2014, the European Society of Cardiology proposed a new risk stratification method based on a risk prediction model (HCM Risk-SCD) that estimates the 5-year risk of SCD. The aim was to externally validate the 2014 European Society of Cardiology recommendations in a geographically diverse cohort of patients recruited from the United States, Europe, the Middle East, and Asia.

METHODS: This was an observational, retrospective, longitudinal cohort study.

RESULTS: The cohort consisted of 3703 patients. Seventy three (2%) patients reached the SCD end point within 5 years of follow-up (5-year incidence, 2.4% [95% confidence interval {CI}, 1.9–3.0]). The validation study revealed a calibration slope of 1.02 (95% CI, 0.93–1.12), C-index of 0.70 (95% CI, 0.68–0.72), and D-statistic of 1.17 (95% CI, 1.05–1.29). In a complete case analysis (n= 2147; 44 SCD end points at 5 years), patients with a predicted 5-year risk of <4% (n=1524; 71%) had an observed 5-year SCD incidence of 1.4% (95% CI, 0.8–2.2); patients with a predicted risk of ≥6% (n=297; 14%) had an observed SCD incidence of 8.9% (95% CI, 5.96–13.1) at 5 years. For every 13 (297/23) implantable cardioverter defibrillator implantations in patients with an estimated 5-year SCD risk ≥6%, 1 patient can potentially be saved from SCD.

CONCLUSIONS: This study confirms that the HCM Risk-SCD model provides accurate prognostic information that can be used to target implantable cardioverter defibrillator therapy in patients at the highest risk of SCD.

Full author list is available on page 1022.

Key Words: cardiomyopathy, hypertrophic ■ death, sudden, cardiac ■ defibrillators, implantable ■ forecasting ■ risk assessment

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Clinical Perspective

What Is New?

- This is a large, international, multicenter study designed to validate the 2014 European Society of Cardiology guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy.
- The guidelines discriminate high- from low-risk patients reasonably well.
- There is a good agreement between predicted risk and subsequent events.

What Are the Clinical Implications?

- Patients with a 5-year sudden cardiac death risk ≥6% should be offered an implantable cardioverter defibrillator.
- Patients with a 5-year sudden cardiac death risk ≤4% should be regularly reassessed.
- In intermediate-risk patients (5-year risk of >4% to <6%), an implantable cardioverter defibrillator may be considered following an appraisal of the lifelong risks and benefits of device therapy.

Hypertrophic cardiomyopathy (HCM) causes sudden cardiac death (SCD) in young and otherwise well individuals.[1,2] Prophylactic treatment with implantable cardioverter defibrillators (ICDs) is the current standard of care for people with HCM deemed to be at high risk of SCD, but the identification of individuals most likely to benefit from device implantation is challenging.[1,2] In 2014, the European Society of Cardiology (ESC) proposed a new approach to risk prediction that uses a clinical risk tool (HCM Risk-SCD) to estimate a 5-year risk of SCD. Although internally validated in a large multicenter cohort,[3] articles published since the ESC recommendations have been inconsistent with respect to the performance of the ESC guidelines in different populations.[4–7] The aim of this study was to validate the 2014 ESC recommendations in a large, geographically diverse cohort recruited from centers in the United States, Europe, the Middle East, and Asia.

METHODS

Study Design

This international EVIDENCE-HCM study (External Validation Study of the 2014 European Society of Cardiology Guideline on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy) used a retrospective, multicenter, longitudinal cohort of patients. The HCM Risk-SCD model was statistically validated and the clinical impact of the 2014 ESC SCD risk stratification guidelines examined using SCD end points within 5 years of baseline clinical evaluation.

The study conforms to the principles of the Declaration of Helsinki. The sponsors of this study did not have a role in study design, data collection, analysis, or interpretation. Drs O'Mahony, Omar, Jichi, and Elliott had access to all data and final responsibility for submission of the manuscript. The authors from each participating center guarantee the integrity of data from their institution and had approval from a local ethics committee/internal review board. Subjects gave informed consent in accordance to local protocol. All investigators have agreed to the manuscript as written. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The study cohort consisted of consecutively evaluated patients with HCM at 14 participating centers in the United States, Europe, the Middle East, and Asia (Table I in the online-only Data Supplement). Included patients were evaluated between 1970 and 2014 (most patients [69%] were evaluated from 2000 onward; Figure I in the online-only Data Supplement). None of the patients were included in the original HCM Risk-SCD development study.[3] Only adult patients (≥16 years of age) without prior ventricular fibrillation or sustained ventricular tachycardia were studied.

HCM was defined as a maximum left ventricular wall thickness (MWT) ≥15 mm unexplained by abnormal loading conditions[8] or in accordance with published criteria for the diagnosis of disease in relatives of patients with unequivocal disease.[9] Patients known to have metabolic diseases or syndromic causes of HCM were excluded.

Patient Assessment and Data Collection

Patients underwent clinical assessment, pedigree analysis, physical examination, ECG (resting and ambulatory), and transthoracic echocardiography. Data were collected independently at each participating center using the same methodology.

Predictor Variables and Calculation of 5-Year Risk of SCD

The following predictor variables were recorded at the time of first evaluation at each participating center:

1. Age at time of evaluation (years)
2. Family history of SCD in ≥1 first-degree relatives <40 years of age or SCD in a first-degree relative with confirmed HCM (post- or antemortem diagnosis) at any age
3. MWT in the parasternal short- and long-axis plane using 2-dimensional echocardiography (mm)
4. Left atrial diameter by M-Mode or 2-dimensional echocardiography in the parasternal long-axis plane (mm)
5. Maximal instantaneous left ventricular outflow tract gradient ($LVOTg_{max}$) at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using continuous-wave Doppler echocardiography (mm Hg)
6. Nonsustained ventricular tachycardia defined as ≥3 consecutive ventricular beats at a rate of ≥120 beats per minute and <30 s in duration on Holter monitoring (minimum duration 24 hours) at or before first evaluation

7. Unexplained syncope at or before first evaluation

The 5-year risk of SCD was calculated using the following equation[3]:

$$\hat{P}_{SCD\ at\ 5\ years} = 1 - 0.998^{\exp(PI)}$$

where *PI* is the prognostic index = 0.15939858×MWT – 0.00294271×MWT^2 + 0.0259082×left atrial diameter + 0.00446131×LVOTg$_{max}$ + 0.4583082×family history of SCD + 0.82639195×nonsustained ventricular tachycardia + 0.71650361×unexplained syncope – 0.01799934×age.

In keeping with clinical practice and the 2014 ESC recommendations,[10] patients with extreme clinical characteristics who were underrepresented in the published development cohort were not used for validation but are reported separately. The extreme clinical characteristics were defined a priori as left atrial diameter >67 mm, LVOTg$_{max}$ >154 mm Hg, MWT >35 mm, or age >80 years. Such patients formed ≤1% of the original development cohort.[3]

Study End Point

The study end point was SCD or an equivalent event. SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1 hour of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms.[11] Aborted SCD during follow-up and appropriate ICD shock therapy were considered equivalent to SCD.[12–17] As in previous studies, ICD shocks were considered appropriate if the treated tachyarrhythmia was ventricular in origin.[12–17] The cause of death was ascertained by the treating cardiologists at each center by using hospital and primary health care records, death certificates, postmortem reports, and interviews with witnesses. Deaths were assessed without knowledge of HCM Risk-SCD estimates.

General Statistical Methods

All statistical analyses were performed using STATA (version 14). Variables are expressed as mean±SD, median (25th, 75th percentiles), or counts and percentages as appropriate. The follow-up time for each patient was calculated from the date of his or her first evaluation to the date of reaching the study end point, or death from another cause, or to the date of his or her most recent evaluation. The annual event rate was calculated by dividing the number of patients reaching the end point by the total follow-up period for that end point. The cumulative probability for the occurrence of an outcome was estimated using the Kaplan-Meier method.

Missing Data

To determine the degree of bias attributable 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 techniques based on chained equations.[18] All predictors of missingness were included in the multiple imputation model, together with the outcome, all prespecified predictors of the risk model, and the estimate of the cumulative hazard function.[19] A total of 45 imputed data sets were generated, and the estimates were combined using Rubin rules.[20]

HCM Risk-SCD Model Validation

The calibration slope was used to assess the degree of agreement between the observed and predicted hazards of SCD.[21] A value close to 1 suggests good overall agreement. Graphical comparisons of the observed and predicted SCD at 5 years by risk groups (group cutoffs: 0%–2%, 2%–4%, 4%–6%, and >6% 5-year risk of SCD) were performed. The C-index as proposed by Uno and the D-statistic were used to measure how well the model discriminated between patients with high and low risk of SCD.[22,23] A value of 0.5 for the 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 has a value of 0 for the D-statistic, with increasing values indicating greater separation.

Sensitivity Analysis: Septal Reduction Therapy

Patients with drug-refractory symptoms secondary to outflow tract obstruction frequently undergo septal reduction therapy after baseline assessment, which can potentially decrease SCD risk predictions by relieving LVOTg$_{max}$ and reducing MWT.[3] To assess the impact of septal reduction therapy on the predictive performance of the model, HCM Risk-SCD was validated without patients undergoing septal reduction therapy within 5 years of follow-up.

Complete Case Analysis: HCM Risk-SCD and SCD End Points at 5 Years

The incidence of the SCD end point is reported in patients with all the data required to calculate the 5-year SCD risk. SCD end points are examined in 3 categories (<4%, 4% to <6%, ≥6%) based on the calculated 5-year SCD risk and the 2014 ESC guideline recommendations. The clinical implications of ICD implantation with a threshold of ≥4%, ≥5%, and ≥6% were examined by descriptive statistics.

RESULTS

Clinical Characteristics of the Cohort

The study enrolled a total of 3902 patients, including 199 (5%) with extreme clinical characteristics. The validation cohort consisted of 3703 patients; the baseline clinical characteristics are shown in Table 1. The cohort was composed of 87 (2.4%) patients aged <20 years, 278 (7.5%) aged 20 to <30 years, 529 (14.3%) aged 30 to <40 years, 703 (19%) aged 40 to <50 years, 861 (23.3%) aged 50 to <60 years, 806 (21.8%) aged 60 to <70 years, and 439 (11.9%) aged 70 to 80 years. One hundred fifty-one patients (4%) were diagnosed on the

Table 1. Baseline Clinical Characteristics

Baseline Clinical Characteristics	Validation Cohort	Patients With Extreme Characteristics*	HCM Risk-SCD Development Cohort, EHJ 2014
Number of patients	3703	199	3675
Male, n (%)	2241 (61)	89 (45)	2349 (64)
Age, y	52±15	70±19	48±17
NYHA III/IV, n (%)	660 (19)	63 (32)	426 (12)
Prior myectomy, n (%)	77 (2)	5 (3)	34 (1)
Prior alcohol septal ablation, n (%)	23 (0.6)	0	10 (0.3)
Amiodarone, n (%)	297 (8)	17 (9)	468 (13)
ICD, n (%)	123 (3)	7 (4)	42 (1)
Permanent/persistent AF, n (%)	433 (12)	34 (17)	366 (10)
NSVT, n (%)	582 (22)	39 (31)	634 (17)
LA diameter; mm	43±8	49±12	44±8
$LVOTg_{max}$, mm Hg	11 (7, 55)	36 (9, 100)	12 (5, 49)
LVedd, mm	45±7	44±7	45±7
MWT, mm	20±4	23±8	20±5
FS, %	42±10	43±11	41±9
FHSCD, n (%)	620 (17)	19 (10)	886 (24)
Unexplained syncope, n (%)	474 (13)	31 (16)	507 (14)

Values are mean±SD, median (25th, 75th percentiles).

AF indicates atrial fibrillation; EHJ, *European Heart Journal*; FHSCD, family history of sudden cardiac death; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LA, left atrium; LVedd, left ventricular end-diastolic dimension; $LVOTg_{max}$, maximal instantaneous left ventricular outflow tract gradient at rest or Valsalva; MWT, maximal wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; and SCD, sudden cardiac death.

*HCM Risk-SCD is currently not recommended in patients underrepresented in the development cohort (left atrial diameter >67 mm, left ventricular outflow tract gradient >154 mm Hg, maximal wall thickness >35 mm, or age >80 y).

basis of familial criteria.[9] Data on self-reported ethnicity were available in 3177 (86%) patients; the cohort was composed of 2631 white (71%), 385 Asian (10%), and 99 black (3%) patients, and 62 patients of mixed/other ethnicity (2%), with 14% missing data. During follow-up, 397 (11%) patients received an ICD.

SCD End Points During Follow-Up

During a follow-up period of 28 186 patient-years (median, 5.9 [3.0, 10] years; range, 2 days [SCD end point] to 39.6 years [censored]), 159 patients (4%) reached the SCD end point with an annual rate of 0.6% (95% confidence interval [CI], 0.5–0.7). Appropriate ICD shocks contributed 42 SCD end points (26%). Seventy-three (2%) patients reached the SCD end point within 5 years of follow-up, with a 5-year incidence of 2.4% (95% CI, 1.9–3.0). Twenty SCD end points within 5 years occurred in patients with a family history of SCD, but there was no familial clustering of end points (defined as >2 SCDs in individuals from the same family group). The clinical characteristics of patients with and without the SCD end point are shown in Table 2.

Table 2. Baseline Clinical Characteristics of Patients With and Without the SCD End Point at 5 Years of Follow-Up

Baseline Clinical Characteristic	Patients Without SCD End Points n=3630 (98%)	Patients With SCD End Points Within 5 y n=73 (2%)
Male, n (%)	2196 (61)	45 (62)
Age, y	52±15	46±15
NYHA III/IV, n (%)	647 (19)	13 (18)
Myectomy, n (%)	76 (2)	1 (1)
Alcohol septal ablation, n (%)	21 (0.6)	2 (3)
Amiodarone, n (%)	279 (8)	18 (25)
Permanent/persistent AF, n (%)	415 (12)	18 (25)
NSVT, n (%)	558 (22)	24 (44)
LA diameter, mm	43±8	44±7
$LVOTg_{max}$, mm Hg	12 (7, 55)	11 (9, 73)
LVedd, mm	45±7	46±7
MWT, mm	20±4	22±5
FS, %	42±10	43±12
FHSCD, n (%)	600 (17)	20 (27)
Unexplained syncope, n (%)	457 (13)	17 (23)

Values are mean±SD, median (25th, 75th percentiles).

AF indicates atrial fibrillation; FHSCD, family history of sudden cardiac death; FS, fractional shortening; LA, left atrium; LVedd, left ventricular end diastolic dimension; $LVOTg_{max}$, maximal instantaneous left ventricular outflow tract gradient at rest or Valsalva; MWT, maximal wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; and SCD, sudden cardiac death.

Missing Data

Missing data were observed in 6 of the 7 HCM Risk-SCD predictor variables: nonsustained ventricular tachycardia, 30%; $LVOTg_{max}$, 17%; unexplained syncope, 2%; family history of SCD, 2%; left atrial diameter, 10%; and MWT, 0.8%. Complete data for the calculation of HCM Risk-SCD estimates were available in 2147 (58%) patients. Missingness was associated with systolic blood pressure, alcohol septal ablation, myectomy, ethnicity, New York Heart Association III/IV, ICD, pacemaker, amiodarone atrial fibrillation, left ventricular end-diastolic pressure, center, and all-cause mortality.

Model Validation

Validation revealed a calibration slope of 1.02 (95% CI, 0.93–1.12). Figure 1 illustrates a good agreement between the observed and predicted risk of SCD at 5 years, particularly in the low-risk groups. The C-index was 0.70 (95% CI, 0.68–0.72). The D-statistic was 1.17 (95% CI, 1.05–1.29), suggesting that the hazard of SCD is 3.2 times higher in the high-risk group than in the low-risk group as predicted by the model.

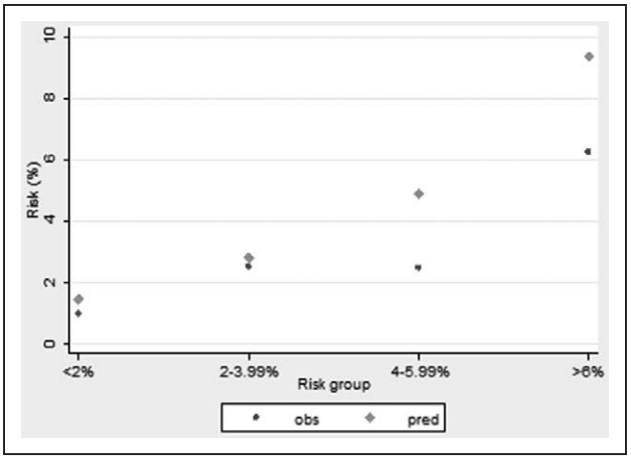

Figure 1. Calibration by risk group.
Circles represent observed (obs) and diamonds represent predicted (pred) probabilities of SCD in 5 years using a random multiple imputation data set. The 4 risk groups (1–4) were created using model-based predicted probabilities (0%–2%, 2%–4%, 4%–6%, and >6% 5-year risk of SCD). These groups are selected for the purposes of validation rather than clinical decision making. SCD indicates sudden cardiac death.

Sensitivity Analysis: Septal Reduction Therapy

A total of 670 (18%) patients had septal reduction therapy during their clinical course (542 myectomies and 150 alcohol septal ablations, with 22 patients having both procedures). Their baseline clinical characteristics are shown in Table 3. Of the 518 patients who had septal reduction therapy within 5 years of their first evaluation, 85% were low- or intermediate-risk and 8 (1.5%) reached the SCD end point within that period. The calibration slope for the model after excluding patients with septal reduction therapy within 5 years of baseline evaluation was 1.09 (95% CI, 0.99–1.18), the C-index was 0.71 (95% CI, 0.68–0.73), and the D-statistic was 1.17 (95% CI, 1.0–1.25).

Complete Case Analysis: HCM Risk-SCD and SCD End Points at 5 Years

The 2147 (58%) patients with complete data had a median 5-year risk of SCD of 2.6% (1.7, 4.4). During a follow-up period of 14496 years (median, 5.4 [2.8, 8.5] years), a total of 96 SCD end points were observed, and 44 patients reached the SCD end point within 5 years (Table 4, Figures 2 and 3). Patients not reaching the SCD end point at 5 years (n=2103) had a median predicted 5-year SCD risk of 2.6% (1.7%, 4.3%), whereas the corresponding calculated risk for those reaching the SCD end point (n=44) was 6.2% (3.2%, 8.6%). The majority (28/44; 64%) of SCD end points within 5 years of baseline evaluation occurred in patients with a 5-year risk of ≥4% (high- and intermediate-risk groups), and although only 14% of patients had a HCM-Risk SCD ≥6% (high-risk group), these patients contributed 52% of SCD end points. Intermediate-risk patients formed 15% of the cohort (n=326) and included 195 patients with a calculated risk of 4.0% to 4.99% with 1 (0.5%) SCD end point within 5 years of baseline evaluation. In the remaining 131 intermediate-risk patients who had a predicted risk of 5.0% to 5.99%, 4 (3%) had a SCD end point within 5 years.

Of the 623 patients with ≥4% SCD risk at 5 years, 28 experienced a SCD end point, which suggests that for every 22 (623/28) ICD implantations in this group, 1 patient can potentially be saved from SCD in that time period. Of the 428 patients with ≥5% SCD risk at 5 years, 27 experienced a SCD end point, which suggests that for every 16 (428/27) ICD implantations, 1 patient can potentially be saved from SCD at 5 years. Of the 297 patients with ≥6% SCD risk at 5 years, 23 experienced a SCD end point, suggesting that for every 13 (297/23) ICD implantations in this group of patients, 1 patient can potentially be saved from SCD at 5 years. Of the 1524 patients with <4% SCD risk at 5 years, 16 experienced a SCD end point, suggesting that for every

Table 3. Baseline Clinical Characteristics of Patients With and Without Septal Reduction

Baseline Clinical Characteristics	Patients Without Septal Reduction Therapy (n=3033)	Patients With Septal Reduction Therapy Before First Evaluation (n=98)	Patients With Septal Reduction Therapy During Follow-Up (n=572)
Time interval between septal reduction and baseline evaluation, y	NA	2.2 (0.4, 8.0)	0.11 (0.01, 1.3)
Male, n (%)	1883 (62)	44 (45)	314 (55)
Age, y	52±15	52±15	51±14
NYHA III/IV, n (%)	319 (11)	27 (26)	315 (55)
Amiodarone, n (%)	216 (7)	21 (22)	60 (10)
Permanent/persistent AF, n (%)	380 (13)	19 (21)	34 (6)
NSVT, n (%)	494 (22)	21 (37)	67 (22)
LA diameter, mm	43±8	47±9	47±8
$LVOTg_{max}$, mm Hg	8 (6, 35)	17 (8, 72)	64 (29, 100)
LVedd, mm	45±7	45±7	43±7
MWT, mm	19±4	19±5	21±4
FS, %	41±10	40±13	45±9
FHSCD, n (%)	508 (17)	18 (19)	94 (17)
Unexplained syncope, n (%)	364 (12)	12 (13)	98 (18)

Values are mean±SD, median (25th, 75th percentiles).
AF indicates atrial fibrillation; FHSCD, family history of sudden cardiac death; FS, fractional shortening; LA, left atrium; LVedd, left ventricular end diastolic dimension; $LVOTg_{max}$, left ventricular outflow tract gradient at rest or Valsalva; MWT, maximal wall thickness; NA, not available; NSVT, nonsustained ventricular tachycardia; and NYHA, New York Heart Association.

Table 4. Events in Patients With Complete Data Set to Calculate HCM Risk-SCD

	Calculated HCM Risk-SCD at 5 y in 2147 Patients: Risk Category		
	<4%	4% to <6%	≥6%
2014 ESC guideline recommendation on ICD implantation	Not recommended if there are no other clinical features that are of proven prognostic importance (III, B)	May be considered in individual patients (IIb, B)	Should be considered (IIa, B)
Patients, n (%)	1524 (71)	326 (15)	297 (14)
SCD end points within 5 y, n (%)	16 (1)	5* (1.5)	23 (7)
5-y incidence of SCD	1.4% (95% CI, 0.8–2.2)	1.8% (95% CI, 0.7–4.3)	8.9% (95% CI, 5.96–13.1)
Annual rate of SCD end point within 5 y of evaluation	0.27% (95% CI, 0.17–0.44)	0.39% (95% CI, 0.16–0.93)	1.92% (95% CI, 1.27–2.88)

CI indicates confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; and SCD, sudden cardiac death.
*Four of 5 patients had a predicted 5-year SCD risk >5%; in total, 428 patients had 5-year risk ≥5% with 27 SCD end points.

95 (1524/16) patients not implanted an ICD, 1 can potentially die suddenly within 5 years.

SCD End Points in Patients With Extreme Clinical Characteristics

A group of 199 patients (199/3902; 5%) had extreme clinical characteristics, including 111 patients aged >80 years, 31 patients with $LVOTg_{max}$ >154 mm Hg, 28 patients with left atrial diameter >67 mm, and 34 patients with MWT>35 mm (5 patients had >1 outlying clinical characteristic). The baseline clinical characteristics of these patients are shown in Table 1.

During a follow-up period of 1102 patient-years (median, 4.5 [2.1, 7.5] years; range, 6 days [SCD end point] to 24.0 years [censored]), 16 patients (8%) reached the SCD end point. Nine (4%) patients reached the SCD end point within 5 years of baseline assessment. The annual rate of SCD end point was 1.5% (95% CI, 0.9–2.4) with a 5-year cumulative incidence of 5.9% (95% CI, 3.0–11.1). Appropriate ICD shocks did not contribute to SCD end points. Seven (7/16; 44%) SCD end points occurred in patients aged >80 years.

DISCUSSION

This study demonstrates that HCM Risk-SCD provides accurate SCD risk estimates in patients recruited in multiple different localities around the world and illustrates the positive impact of the 2014 ESC recommendations on clinical decision making. Specifically, it shows that the risk-benefit ratio for ICD implantation is most favorable in individuals with an estimated 5-year risk of ≥6%.

The clinical usefulness of the 2014 ESC guidelines for sudden death prevention is dependent on the performance of the HCM Risk-SCD tool, and external validation studies are essential to demonstrate the accuracy of its predictions in diverse patient populations. HCM Risk-SCD performance was similar to that reported in the original study and is consistent with several smaller external validation cohorts from Europe and South America.[4–6] An exception is a study of patients from 2 North American centers in which HCM Risk-SCD had a high negative predictive value but was less reliable in predicting long-term outcomes.[7] However, direct comparison with the present analysis is difficult, because the North American study did not report discrimination, calibration, or end points within 5 years of baseline evaluation.[7]

This study shows that HCM Risk-SCD can be used to avoid unnecessary ICD implants in low-risk patients. The large majority of HCM patients had a 5-year risk of SCD of <4%, and the very low SCD end point rate in this patient subgroup, reported in this and other studies,[4,5,7] supports the 2014 ESC recommendation not to implant an ICD in individuals with a low estimated risk.[2] Conversely, patients with a predicted 5-year risk of SCD ≥6% formed a small subgroup that had the highest event rate and the largest absolute number of events.[2] In patients with a high estimated 5-year risk,

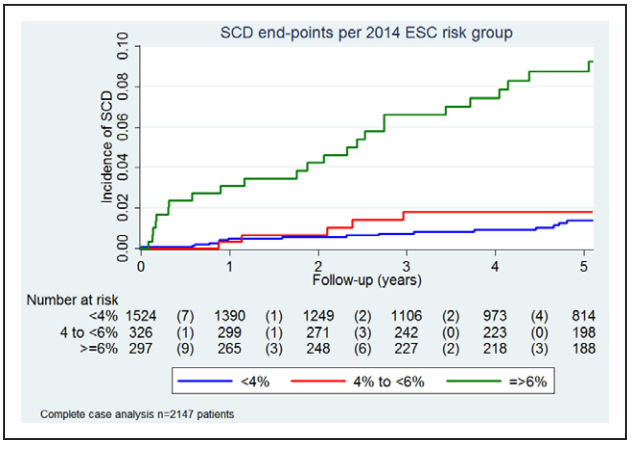

Figure 2. Kaplan-Meier curve showing SCD end points within 5 years of baseline evaluation, stratified according to the estimated 5-year risk of SCD.
Patients with complete data for the calculation of HCM Risk-SCD estimates (n=2147) were classified in 3 risk groups in accordance to the 2014 ESC guidelines (HCM Risk-SCD <4%, 4% to <6%, ≥6%). The at-risk table shows the number of SCD end points in parentheses. ESC indicates European Society of Cardiology; HCM, hypertrophic cardiomyopathy; and SCD, sudden cardiac death.

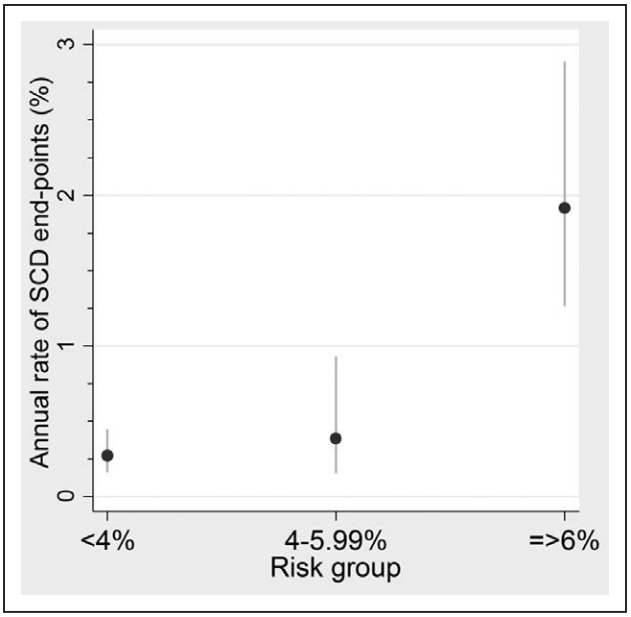

Figure 3. The annual rate of SCD end points within 5 years of baseline evaluation stratified according the estimated 5-year risk of SCD.
The annual risk of SCD end points and the 95% confidence intervals for the three 2014 ESC guidelines risk groups (HCM Risk-SCD <4%, 4% to <6%, ≥6%) are shown (complete case analysis n=2147). ESC indicates European Society of Cardiology; HCM, hypertrophic cardiomyopathy; and SCD, sudden cardiac death.

the predicted event rates were slightly overestimated, but this is less of a problem in clinical practice because this group of patients still had the highest event rate (≥6% at 5 years) and, as a result, have the greatest benefit from prophylactic ICD therapy.

Because there is no consensus on the absolute SCD risk that justifies ICD therapy, there are some patients in whom clinical decision making is more complex and determined by more than a simple estimation of SCD risk. This is reflected in the 2014 ESC guidelines in the form of an intermediate-risk category (5-year risk of ≥4% to <6%) in which an ICD may be considered following a detailed clinical assessment and an appraisal of the lifelong risks and benefits of device therapy. This study suggests that most intermediate-risk patients can be managed conservatively, but ICDs have the potential to prevent some sudden deaths in this subgroup, especially in those with a 5-year risk of ≥5%. The downside of using a lower-risk threshold for ICD implantation is the greater healthcare cost and unnecessary exposure of more individual patients to the long-term complications of devices.

Because patients with HCM are generally young, it is reasonable to conjecture that some will change their risk profile during follow-up, thereby violating one of the model's basic assumptions. To account for this, the 2014 ESC guidelines recommend that patients seek medical attention if their clinical condition changes and that patients should be routinely reassessed every 12 to 24 months.[2] Although it will be challenging, future iterations of the HCM Risk-SCD model may be able to test its performance beyond 5 years if a sufficient number events are observed.

Patients with extreme values for individual risk factors were underrepresented in the original HCM Risk-SCD development cohort,[3] and consequently, the 2014 ESC guidelines do not recommend the use of the model in such patients.[2] Patients with extreme clinical characteristics were also uncommon in this study, which implies that the 2014 ESC guidelines are applicable to most patients seen in clinical practice. Furthermore, most were >80 years of age, a group in whom ICD implantation is frequently inappropriate because of comorbid conditions.

Patients undergoing septal reduction therapy were more frequent in this study (18%) than in the development cohort (9%).[3] Even though septal reduction therapy may have an impact on disease outcomes, the sensitivity analysis in this study suggests that the accuracy of HCM Risk-SCD predictions is not significantly affected by septal reduction therapy in the short term. These data suggest that SCD risk stratification should be undertaken independently but in parallel with the management of symptomatic left ventricular outflow tract obstruction. The small number of SCD end points in this subgroup does not allow an examination of the prognostic impact of septal reduction or a direct comparison of SCD rates following myectomy and alcohol septal ablation.

As with other widely used clinical risk tools, it is essential that HCM Risk-SCD and the 2014 ESC guidelines continue to be the subject of constant reassessment in diverse patient populations to ensure accuracy in varied clinical scenarios. Risk stratification can potentially be improved by examining the incremental predictive value of other patient characteristics such as genotype and myocardial scar burden in future studies.[24,25] Despite the promise of future improvements, there will always be inherent uncertainty exemplified by sudden deaths in apparently low-risk patients and lack of events in high-risk patients with past and present risk stratification strategies.[26,27] No risk stratification strategy will ever be able to predict all sudden deaths, but quantification of risk enhances the shared decision-making process and may aid the development of an effective decision-making tool in the future.[28]

This study has a number of limitations. A retrospective, multicenter design was essential, because the low SCD rate makes prospective validation studies challenging because a large number of patients needs to be followed up for prolonged time periods. Despite the size of the study cohort, there were only 74 SCD end points within 5 years. However, the narrow 95% CIs of

the validation measures suggest that these have been estimated with reasonable precision. This validation study had more missing data than the original development study, but appropriate statistical techniques were used to correct for this. Patients aged 16 to 20 years were relatively underrepresented, and the validity of the model in this population may require further study.

This external validation study shows that the HCM Risk-SCD model and 2014 ESC guidelines provide accurate prognostic information in patients with HCM that can be used to identify patients with a high risk of potentially fatal ventricular arrhythmia in the short to medium term. Although no risk stratification strategy can predict all events, quantification of risk enhances the shared decision-making process and provides the basis for consistent and effective treatment choices.

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