AN INTERNATIONAL EXTERNAL VALIDATION STUDY OF THE 2014 EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINE ON SUDDEN CARDIAC DEATH PREVENTION IN HYPERTROPHIC CARDIOMYOPATHY.

Running title: Sudden death in hypertrophic cardiomyopathy

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CONFLICTS OF INTEREST

J Geske has a consulting relationship (moderate) with Myokardia, Inc. A.Wilde is a member of the scientific advisory board of LilaNova. All other authors have no conflicts of interest to declare.

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Abbreviations:

Hypertrophic cardiomyopathy= HCM

Internal cardioverter defibrillator= ICD

Sudden cardiac death= SCD

Maximal left ventricular wall thickness= MWT

Maximal instantaneous left ventricular outflow tract gradient= $LVOTg_{max}$

FHSCD: Family history of sudden cardiac death

LAd: Left atrial diameter

NSVT: non-sustained ventricular tachycardia

ABSTRACT

Background

Implantable cardioverter defibrillators (ICD) are recommended in patients with HCM deemed to be at high risk of sudden cardiac death (SCD) but identification of such individuals remains challenging. In 2014 the European Society of Cardiology (ESC) proposed a new risk stratification method based on a risk prediction model (HCM Risk-SCD) which estimates the 5-year risk of SCD.

Objectives

To externally validate the 2014 ESC recommendations in a geographically diverse cohort of HCM patients recruited from North America, Europe, The Middle East and Asia.

Methods

Observational, retrospective, longitudinal cohort study.

Results

The validation cohort consisted of 3703 patients. During a follow-up period of 28,186 patient years (median 5.9 years) 159 patients (4%) reached the SCD end-point with an annual rate of 0.6% (95% CI 0.5, 0.7). 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). Validation revealed a calibration slope of 1.02 (95% CI 0.93 to 1.12); C-index was 0.70 (95% CI 0.68 to 0.72) and D-statistic was 1.17 (95% CI 1.05 to 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. There were 23 SCD end-points in patients with ≥6% SCD risk suggesting that for every 13 (297/23) ICD implantations in this group, 1 patient can potentially be saved from SCD at 5 years.

Conclusions

HCM Risk–SCD provides accurate prognostic information and by preferentially targeting the highest risk group may help reduce unnecessary ICD implantation.

Keywords: hypertrophic cardiomyopathy; sudden cardiac death; implantable cardioverter defibrillator; risk prediction model

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a relatively common cardiac condition that can cause sudden cardiac death (SCD) in young and otherwise well individuals.(1,2) Prophylactic treatment with implantable cardioverter defibrillators (ICD) 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 remains 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 five-year risk of sudden cardiac death. Although internally validated in a large multi~~centre~~center cohort,(3) papers 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 ~~centre~~centers in North America, Europe, The Middle East and Asia.

METHODS

Study design

The study used data from a retrospective, international multi-~~centre~~center, longitudinal cohort of ~~HCM~~ patients with HCM. 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 Helsinki declaration. The sponsors of this study did not have a role in study design, data collection, analysis or interpretation. COM, RO, FJ, and PE had access to all data and final responsibility for submission of the manuscript. The authors from each participating ~~centre~~center guarantee the integrity of data from their institution and had approval from a ~~the appropriate~~ local ethics committee. All investigators have agreed to the manuscript as written.

Study population

The study cohort consisted of consecutively evaluated patients with HCM at 14 participating ~~centre~~centers in the USA, Europe, the Middle East and Asia (supplementary table 1). The patients were enrolled between 1970 and 2014 and none 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) ≥15mm 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

~~All patients had planned clinical reviews every 6-12 months or earlier if there was a change in symptoms.~~ Patients underwent clinical assessment, pedigree analysis, physical examination, electrocardiography (resting and ambulatory) and transthoracic echocardiography. Data were collected independently at each participating ~~centre~~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 ~~centre~~center:

1. Age (years)

2. Family history of SCD (FHSCD) in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM (post or ante-mortem diagnosis) at any age.

3. MWT in the parasternal short and long-axis plane using 2-D echocardiography (mm)

4. Left atrial diameter (LAd) by M-Mode or 2D 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 (mmHg)

6. Non-sustained ventricular tachycardia (NSVT) defined as ≥3 consecutive ventricular beats at a rate of ≥120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to first evaluation.

7. Unexplained syncope at or prior to first evaluation.

The 5 year risk of SCD was calculated using the following equation:

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

where Prognostic Index = 0.15939858*MWT - 0.00294271*MWT^2 + 0.0259082* LAd + 0.00446131*$LVOTg_{max}$ + 0.4583082*FHSCD + 0.82639195*NSVT + 0.71650361*Unexplained syncope - 0.01799934*Age.(3)

In keeping with clinical practice and the 2014 ESC recommendations (http://www.doc2do.com/hcm/webHCM.html), patients with extreme clinical characteristics who were under-represented in the published development cohort ~~(left atrial diameter >67mm, left ventricular outflow tract gradient >154mmHg, maximal wall thickness >35mm or age >80 years)~~ were not used for validation but are reported separately. The extreme clinical characteristics were defined a priori as ~~(~~left atrial diameter >67mm, left ventricular outflow tract gradient >154mmHg, maximal left ventricular wall thickness >35mm or age ~~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 one hour of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms.(10) Aborted SCD during follow-up and appropriate ICD shock therapy were considered equivalent to SCD. (11-16) ICD shocks were considered appropriate if the treated tachyarrhythmia was ventricular in origin as in previous studies.(11-16) The cause of death was ascertained by the treating cardiologists at each ~~centre~~center using hospital and primary health care records, death certificates, post-mortem reports and interviews with witnesses (relatives and physicians). Deaths were assessed without knowledge of HCM Risk-SCD estimates.

General statistical methods

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

Missing data

To determine the degree of bias due to missing data, the characteristics of patients with missing information were compared with those with complete information. Logistic regression was used to identify the predictors of missingness. Data were assumed to be missing at random and values for the missing predictors were imputed using multiple imputation techniques based on chained equations.(17) All predictors of missingness were included in the multiple imputation model, together with the outcome, all pre-specified predictors of the risk model, and the estimate of the cumulative

hazard function.(18) A total of 45~~??~~ imputed data sets were generated and the estimates were combined using Rubin's rules.(19)

HCM Risk-SCD model validation

The calibration slope was used to assess the degree of agreement between the observed and predicted hazards of SCD.(20) A value close to 1 suggests good overall agreement. Graphical comparisons of the observed and predicted SCD at 5 years by risk groups (group cut-offs: 0-2%, 2-4%, 4-6% and >6% 5-year risk of SCD) were performed. The C-index as proposed by Uno and D-statistic were used to measure how well the model discriminated between patients with high and low risk of SCD.(21,22) A value of 0.5 for C-index indicates no discrimination and a value equal to 1 indicates perfect discrimination. The D-statistic quantifies the observed separation between subjects with low and high predicted risks as predicted by the model and can be interpreted as the log hazard ratio for having SCD between the low and high risk groups of patients. A model with no discriminatory ability has ~~will produce~~ a value of 0 for D-statistic, with increasing values indicating greater separation.

Sensitivity analysis: septal reduction therapy

~~Additional model validation was performed after excluding patients undergoing septal reduction therapy.~~ Patients with drug refractory symptoms secondary to outflow tract obstruction frequently undergo septal reduction therapy after baseline assessment ~~Septal reduction therapy (myectomy or alcohol septal ablation~~ which ~~)~~ can potentially decrease~~reduce~~ SCD risk predictions by relieving $LVOTg_{max}$~~,~~ and reducing MWT~~ and LA size which are predictors of SCD risk~~. (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 necessary data required to calculate the 5-year SCD risk. SCD end-points are examined in three 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~~calculating the number needed to treat to prevent one SCD end-point~~.

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; ~~and~~ the baseline clinical characteristics are shown in table 1. One hundred and fifty-one patients (4%) were diagnosed on the basis of familial criteria.(9) 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% 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). The clinical characteristics of patients with and without the SCD end-point are shown in table 2.

Missing data

Missing data were observed in six of the seven HCM Risk-SCD predictor variables: NSVT 30%, $LVOTg_{max}$ 17%, unexplained syncope 2%, FHSCD 2%, LAd 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, NYHA 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 ~~1.017 (95% CI: 0.893 to 1.142)~~ 1.022 (95% CI 0.9328 to 1.1216). Figure 1 illustrates a good agreement between the observed and predicted risk of sudden cardiac death at 5 years, particularly in the low risk groups. The C-index was ~~0.698 (95% CI: 0.671 to 0.725)~~ 0.70697 (95% CI 0.6875 to 0.7219). The D-statistic was ~~1.165 (95% CI: 1.004 to 1.327)~~ 1.1766 (95% CI 1.0546 to 1.2985) suggesting that the hazard of SCD is 3.2 times higher in the high risk group compared to the hazard in the low risk group as predicted by the model.

Sensitivity analysis: septal reduction therapy

A total of 670 (18%) patients had septal reduction therapy at some point during their clinical course (542 myectomies and 150 alcohol septal ablations, with 22 patients having both procedures) ~~and most (85%) were low or intermediate risk~~. The baseline clinical characteristics are shown in table 4. ~~During follow-up 20 patients who had septal reduction therapy reached the SCD end-point with an annual rate of 0.4% (95% CI 0.3, 0.6) post septal reduction therapy.~~ Of the 518 patients who had septal reduction therapy within 5 years of 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 1.090.98 (95% CI: 0.9985, 1.118), the C-index was 0.7169 (95%: CI 0.668, 0.723) and D-statistic was 1.172 (95% CI: 1.00.95, 1.295).

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 14,496 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 (figure 2). 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% (figure 3 and table 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%), whilst the corresponding calculated risk ~~figures~~ for those reaching the SCD end-point (n=44) was~~ere~~ 6.2% (3.2%, 8.6%).

~~For every 22 ICD implantations in patients with ≥4% 5 year SCD risk, 1 patient can potentially be saved from SCD at 5 years. At an ICD implantation threshold of ≥5 and ≥6%, 1 patient can potentially be saved for every 16 and 13 ICD implantations respectively.~~ 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 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 ~~This group included~~ 111 patients aged >80years, 31 patients with $LVOTg_{max}$ >154mmHg, 28 patients with LAd >67mm and 34 patients with MWT>35mm (5 patients had more than one outlying clinical characteristic). The baseline clinical characteristics of these patients are shown in table 1.

During a follow-up period of 1,102 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.

Complete data to calculate HCM Risk-SCD were available in 109 (65%) patients with extreme clinical characteristics. Of the 74 (63~~7~~%) patients with a 5-year risk of <4%, two reached the SCD end-point within 5 years of baseline assessment (aged 82 and 47 years, both with significant left ventricular outflow tract obstruction).There were no SCD end-points within 5 years of evaluation in 21 (11%) high risk patients (~~with a~~ ≥6% 5-year risk) or in ~~the~~ 14 (7%) intermediate risk patients ~~with a~~ (4% to <6% 5-year risk). ~~Of the 74 (37%) patients with a 5-year risk of <4%, two reached the SCD end-point within 5 years of baseline assessment (aged 82 and 47 years, both with significant left ventricular outflow tract obstruction).~~

MWT>35mm was present in 34 patients (mean age 41±18 years, 19 (56%) male). During a follow-up period of 271 patient years (median 7.1 (4.1, 12.1) years), 4 patients reached the SCD end-point. There was a single SCD end-point within 5 years of assessment with a 5 year incidence of 3.2% (95% CI: 0.5, 21). None of the patients with a ~~All~~ MWT>35mm ~~patients~~ who reached the SCD end-point ~~did not~~ had~~ve~~ sufficient data to calculate the 5 year risk of SCD.

DISCUSSION

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 ~~outside the original development cohort~~. This study demonstrates that HCM Risk-SCD provides reasonably accurate SCD risk estimates in patients recruited in multiple different localities around the World and illustrates ~~. The study also shows~~ the positive ~~clinical~~ impact of the 2014 ESC recommendations on clinical decision making ~~ICD implantation by targeting the highest risk group and attempting to minimise unnecessary ICD implantation~~.

In this external validation study, HCM Risk-SCD performance was similar to that reported in the original study and is consistent ~~n keeping~~ with other several smaller external validation ~~studies in~~ cohorts from Europe and South America.(4-6) An exception is a ~~In a~~ study of patients from two North

American ~~centre~~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 ~~other studies~~ is difficult as the North American study did not report discrimination, calibration or end-points within 5 years of baseline evaluation.(7)

~~This study shows that the model allows effective clinical decision making.~~ 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 ~~in this study~~ 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 which had the highest event rate and the largest absolute number of events .(2) In patients with a high estimated 5 year risk, the predicted event rates were slightly overestimated, but this is less of a problem in clinical practice as this group of patients still had the highest event rate (≥6% at 5 years) and as a result the greatest potential benefit from prophylactic ICD therapy.~~. Targeting of this group for prophylactic ICD therapy prevents unnecessary ICD implantation and is likely to yield greatest long-term benefit.~~

Since 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 an 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 shows that ICDs have the potential to prevent some sudden deaths in this subgroup, especially in those with a 5-year risk of ≥5%. ~~Approximately one in seven patients had intermediate risk (5-year risk of ≥4% to <6%) which, depending on individual clinical characteristics and social context, might justify consideration of an ICD. This eventuality was recognised in the 2014 ESC guidelines and this study shows that ICDs have the potential to prevent some sudden deaths in this subgroup, especially in patients 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 individual patients to the long-term complications of devices~~The downside of using a lower risk threshold for ICD implantation is a higher number needed to treat with its attendant effects on healthcare cost and individual exposure to the long term effects of device implantation~~.

P~~HCM p~~atients 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 use of the model in such patients.(2) Patients with extreme clinical characteristics were 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 due to co-morbid 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.

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 ~~Even though no risk stratification strategy will ever be able to predict SCD with absolute certainty, risk prediction~~ can potentially be ~~further~~ improved by examining the incremental predictive value of other patient characteristics such as genotype and myocardial scar burden in future studies.(23,24) 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.(25,26) 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.(27)

This study has a number of limitations. A retrospective design was essential since the low SCD rate makes prospective validation studies challenging as large number of patients need to be followed up for prolonged time periods. This validation study had more missing data that the original development study but appropriate statistical techniques were used to overcome this problem.

CONCLUSIONS

This external validation study shows that the HCM Risk-SCD model and 2014 ESC guidelines provide accurate prognostic information in patients with HCM which can be used to identify patients with a high risk of potentially fatal ventricular arrhythmia in the short to medium term~~This external validation study shows that HCM Risk-SCD provides accurate prognostic information in patients with HCM. The framework set out by the 2014 ESC guidelines preferentially targets the highest risk group and helps reduce unnecessary ICD implantation.~~. While 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.

PRESPECTIVES

Competency in medical knowledge 1:

Hypertrophic cardiomyopathy (HCM) in an inherited disease associated with sudden cardiac death (SCD) secondary to ventricular fibrillation. An Implantable Cardioverter Defibrillator (ICD) is recommended for secondary prevention in survivors of sudden death and for primary prevention in high risk patients.

Competency in medical knowledge 2:

All patients with HCM should undergo SCD risk stratification with a family pedigree, ambulatory ECG monitoring and a transthoracic echocardiogram.

Competency in patient care:

The 2014 ESC guidelines recommend stratification using a risk prediction model (HCM Risk-SCD) which uses 7 readily available clinical parameters (maximal wall thickness, non-sustained ventricular tachycardia, family history of SCD, left atrial diameter, left ventricular outflow tract gradients, age, unexplained syncope) to estimate the 5-year risk of SCD.

Competency in interpersonal skills and communication skills:

It is important to discuss with HCM patients the risk of SCD and the uncertainties of risk stratification.

Translational outlook 1:

This study demonstrates that HCM Risk-SCD provides accurate SCD risk estimates in patients recruited in different localities around the World. Most HCM patients are low risk and require regular reassessment. Most SCD occur in patients with a 5-year risk of >6%.

Translational outlook 2:

Additional research is needed to improve SCD risk stratification by examining the incremental predictive value of additional parameters such as genetic information and imaging markers of myocardial fibrosis.

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~~*To be completed*~~

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~~CONFLICTS OF INTEREST~~

~~All other authors have no conflicts of interest to declare.~~

~~ACKNOWLEDGEMENTS~~

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~~ETHICS APPROVAL~~

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Con formato: Sangría: Izquierda: 0 cm, Sangría francesa: 1,27 cm, Espacio Después: 0 pto, Punto de tabulación: 0,95 cm, Derecha + 1,27 cm, Izquierda

FIGURE LEGENDS

Figure 1. Calibration by risk group.

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

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 three 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.

Figure 3: The relative contribution of each risk group to SCD end-points

Patients with complete data for the calculation of HCM Risk-SCD estimates (n= 2147) were classified in three risk groups in accordance to the 2014 ESC guidelines (HCM Risk-SCD <4%, 4% to <6%, ≥6%). Even though only 14% of patients have a HCM-Risk SCD ≥6%, these patients contribute 52% of SCD end-points.

Table 1: Baseline clinical characteristics

	Clinical characteristics	Validation cohort	Patients with extreme characteristics*	HCM Risk-SCD development cohort, EHJ 2014
BASELINE ASSESSMENT	*Number of patients*	3703	199	3675
	Male	2241 (61%)	89 (45%)	2349 (64%)
	Age; years	52 ±15	70 ±19	48 ±17
	NYHA III/IV	660 (19%)	63 (32%)	426 (12%)
	Prior Myectomy	77 (2%)	5 (3%)	34 (1%)
	Prior Alcohol septal ablation	23 (0.6%)	0	10 (0.3%)
	Amiodarone	297 (8%)	17 (9%)	468 (13%)
	ICD	123 (3%)	7 (4%)	42 (1%)
	Permanent /persistent AF	433 (12%)	34 (17%)	366 (10%)
	NSVT	582 (22%)	39 (31%)	634 (17%)
	LA diameter; mm	43±8	49±12	44±8
	$LVOTg_{max}$; mmHg	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%)

NYHA: New York Heart Association, ICD: implantable cardioverter defibrillator, AF: Atrial fibrillation, NSVT: non-sustained ventricular tachycardia, LA: left atrium, $LVOTg_{max}$: maximal instantaneous left ventricular outflow tract gradient at rest or Valsalva, LVedd: left ventricular end diastolic dimension, MWT: maximal wall thickness, FS: fractional shortening, FHSCD: family history of sudden cardiac death, SCD: sudden cardiac death.*HCM Risk-SCD is currently not recommended in patients underrepresented in the development cohort (left atrial diameter>67mm, left ventricular outflow tract gradient>154mmHg, maximal wall thickness>35mm or >80 years)

Table 2: The 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 years n=73 (2%)**
Male	2196 (61%)	45 (62%)
Age; years	52±15	46±15
NYHA III/IV	647 (19%)	13 (18%)
Myectomy	76 (2%)	1 (1%)
Alcohol septal ablation	21 (0.6%)	2 (3%)
Amiodarone	279 (8%)	18 (25%)
Permanent /persistent AF	415 (12%)	18 (25%)
NSVT	558 (22%)	24 (44%)
LA diameter; mm	43±8	44±7
$LVOTG_{max}$; mmHg	12 (7, 55)	11 (9, 73)
LVedd; mm	45±7	46±7
MWT; mm	20±4	22±5
FS; %	42±10	43±12
FHSCD	600 (17%)	20 (27%)
Unexplained syncope	457 (13%)	17 (23%)

NYHA: New York Heart Association, ICD: implantable cardioverter defibrillator, AF: Atrial fibrillation, NSVT: non-sustained ventricular tachycardia, LA: left atrium, *$LVOTg_{max}$*: maximal instantaneous left ventricular outflow tract gradient at rest or Valsalva, LVedd: left ventricular end diastolic dimension, MWT: maximal wall thickness, FS: fractional shortening, FHSCD: family history of sudden cardiac death, SCD: sudden cardiac death.

Table 3: Events in patients with complete dataset to calculate HCM Risk-SCD

	Calculated HCM Risk-SCD at 5 years 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)
Number of patients	*1524 (71%)*	326 (15%)	297 (14%)
SCD end-points within 5 years	*16 (1%)*	5* (1.5%)	23 (7%)
5 year 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)

*4/5 patients had a predicted 5-year SCD risk >5%; in total, 428 patients had 5-year risk ≥5% with 27 SCD end-points

Table 4:

Baseline clinical characteristic	**Patients without septal reduction therapy (n=3033)**	**Patients with septal reduction therapy prior to first evaluation (n=98)**	**Patients with septal reduction therapy during follow-up (n=572)**
Time interval between septal reduction and baseline evaluation (years)	NA	2.2 (0.4, 8.0)	0.11 (0.01, 1.3)
Male	1883 (62%)	44 (45%)	314 (55%)
Age; years	52±15	52±15	51±14
NYHA III/IV	319 (11%)	27 (26%)	315 (55%)
Amiodarone	216 (7%)	21 (22%)	60 (10%)
Permanent /persistent AF	380 (13%)	19 (21%)	34 (6%)
NSVT	494 (22%)	21 (37%)	67 (22%)
LA diameter; mm	43±8	47±9	47±8
$LVOTG_{max}$; mmHg	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	508 (17%)	18 (19%)	94 (17%)
Unexplained syncope	364 (12%)	12 (13%)	98 (18%)

NYHA: New York Heart Association, ICD: implantable cardioverter defibrillator, AF: Atrial fibrillation, NSVT: non-sustained ventricular tachycardia, LA: left atrium, *$LVOTg_{max}$*: left ventricular outflow tract gradient at rest or Valsalva, LVedd: left ventricular end diastolic dimension, MWT: maximal wall thickness, FS: fractional shortening, FHSCD: family history of sudden cardiac death.

Figure 1

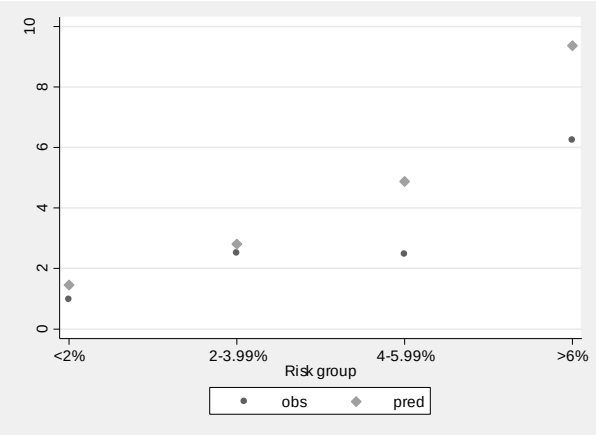

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Figure 2

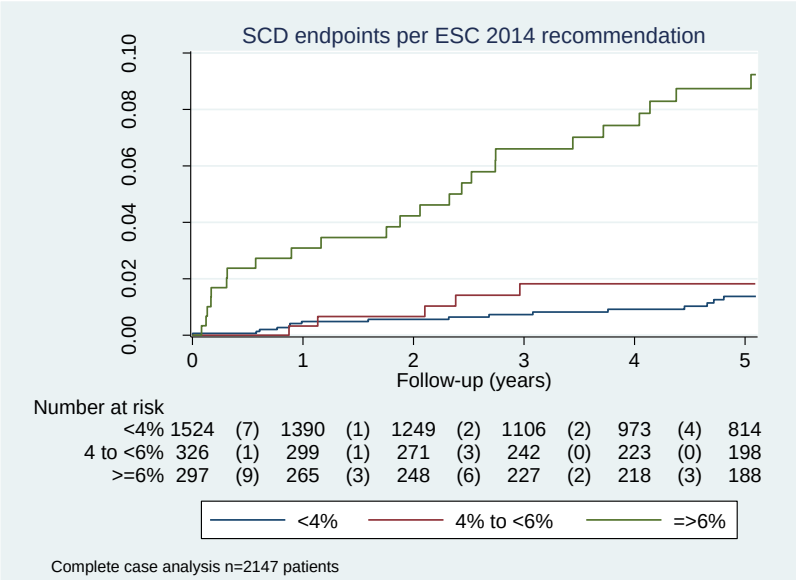

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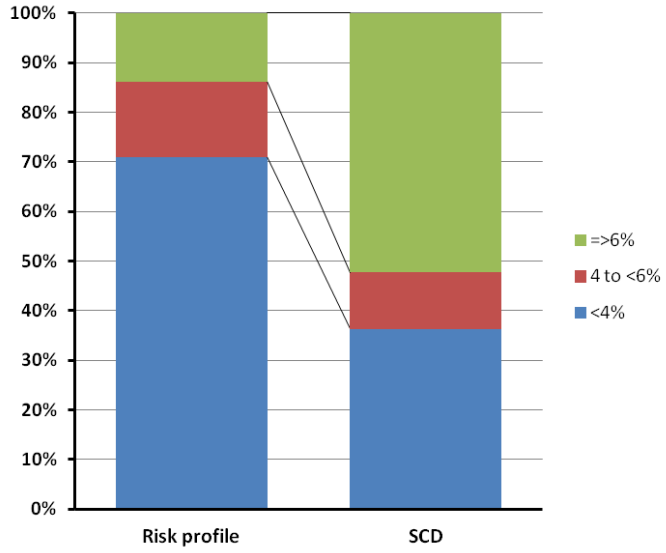
Figure 3



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