10.1161/CIRCULATIONAHA.117.030437

An International External Validation Study of the 2014 European Society of Cardiology Guideline on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (Evidence from HCM)

Running Title: *O'Mahony et al.; Sudden Death in Hypertrophic Cardiomyopathy*

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Abstract

***Background*—**Identification of people with hypertrophic cardiomyopathy (HCM) who are at risk of sudden cardiac death (SCD) and require prophylactic implantable cardioverter defibrillator (ICD) is 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. The aim was to externally validate the 2014 ESC recommendations in a geographically diverse cohort of patients recruited from North America, 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% CI 1.9, 3.0)]. The validation study revealed a calibration slope of 1.02 (95% CI 0.93 to 1.12); C-index 0.70 (95% CI 0.68 to 0.72) and D-statistic 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. For every 13 (297/23) ICD 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 which can be used to target ICD therapy in patients at the highest risk of SCD.

Key Words: hypertrophic cardiomyopathy; sudden cardiac death; ventricular fibrillation; implanted cardioverter defibrillator

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Clinical Perspective

What is new?

- This is a large, international, multi-centre study designed to validate the 2014 European Society of Cardiology guidelines on sudden cardiac death (SCD) prevention in hypertrophic cardiomyopathy (HCM)
- 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 SCD risk ≥6% should be offered an ICD
- Patients with a 5-year SCD risk ≤4% should be regularly re-assessed
- In intermediate risk patients (5-year risk of >4% to <6%) an ICD 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 (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 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 five-year risk of sudden cardiac death. Although internally validated in a large multicentre 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 centres in North America, Europe, The Middle East and Asia.

Methods

Study design

This international **e**xternal **val**i**d**ation study of the 2014 **E**uropean Society of Cardiology guideline on sudde**n** **c**ardiac d**e**ath prevention in **h**ypertrophic **c**ardio**m**yopathy (EVIDENCE-HCM) used a retrospective, multi-center, 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 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 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 USA, Europe, the Middle East and Asia (supplementary table 1). Included patients were evaluated between 1970 and 2014 (most patients (69%) were evaluated from 2000 onwards; supplementary figure 1). 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) ≥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

Patients underwent clinical assessment, pedigree analysis, physical examination, electrocardiography (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 (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[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* LAd + 0.00446131*$LVOTg_{max}$ + 0.4583082*FHSCD + 0.82639195*NSVT + 0.71650361*Unexplained syncope - 0.01799934*Age.

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 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 >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] As in previous studies, ICD shocks were considered appropriate if the treated tachyarrhythmia was ventricular in origin.[11-16] The cause of death was ascertained by the treating cardiologists at each center using hospital and primary health care records, death certificates, post-mortem reports and interviews with witnesses. 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 a value of 0 for 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 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.

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 <20 years of age, 278 (7.5%) patients 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 and fifty-one patients (4%) were diagnosed on the 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%), 99 black (3%) 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% 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 FHSCD but there was no familial clustering of end-points (defined as >2 SCD in individuals from the same family group). 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, centre and all cause mortality.

Model validation

Validation revealed a calibration slope of 1.02 (95% CI 0.93 to 1.12). 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 0.70 (95% CI 0.68 to 0.72). The D-statistic was 1.17 (95% CI 1.05 to 1.29) 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 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 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 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 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 (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%), whilst 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 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 >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.

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 favourable 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 other several smaller external validation cohorts from Europe and South America.[4-6] An exception is a study of patients from two North American centres 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 as 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 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 have the greatest benefit from prophylactic ICD therapy.

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 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.

As 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 re-assessed every 12-24 months.[2] While 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 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 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. 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.[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, multi-center 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. 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 that the original development study, but appropriate statistical techniques were used to correct for this. Patients aged 16-20 years were relatively underrepresented and the validity of the model in this population may require further study.

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. 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.

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Sources of Funding

This work was undertaken at University College London (UK) (London, UK) and St Bartholomew's Hospital (London, UK) which received a proportion of funding from the United Kingdom Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. EA and VF were supported by the Italian Ministry of Health (project title: "Diagnosis and Treatment of Hypertrophic Cardiomyopathies", n°RF-PSM-2008-1145809) and MAGICA (MAlattie GenetIche CArdiovascolari) Onlus Charity. AW gratefully acknowledges the support from the Netherlands CardioVascular Research Initiative, the Dutch Heart Foundation, the Dutch Federation of University Medical Centres, the Netherlands

Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences. PGP was supported by Instituto de Salud Carlos III [grants PI14/0967 and RD012/0042/0066] through the Plan Estatal de I+D+I 2013-2016 – European Regional Development Fund (FEDER) "A way of making Europe". MDG was supported by Instituto de Salud Carlos III. IO, FC and IT gratefully acknowledge support from the Italian Ministry of Health (Left ventricular hypertrophy in aortic valve disease and hypertrophic cardiomyopathy: genetic basis, biophysical correlates and viral therapy models" (RF-2013-02356787) and NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy) and by the ToRSADE project (FAS-Salute 2014, Regione Toscana). OPG received research support from the British Heart Foundation (FS/12/86/29841) and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. St. Bartholomew's Hospital is a member of European Reference Network on Rare and Complex Diseases of the Heart (Guard-Heart) (http://guardheart.ern-net.eu).

Disclosures

JG and PE have a consulting relationship (moderate) with Myokardia. AW is a member of the scientific advisory board of LilaNova. FC reports grants from Boston Scientific, Amicus, Genzyme, and SMART Solutions. IT reports grants from Boston Scientific. IO reports grants from Myokardia, grants and personal fees from Genzyme, grants and personal fees from Shire outside the submitted work. All other authors have no conflicts of interest to declare.

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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. The baseline clinical characteristics of patients with and without septal reduction

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.

Table 4. 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)
Annual rate of SCD end-point within 5 years 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)

*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

Figure Legends

Figure 1. Calibration by risk group.

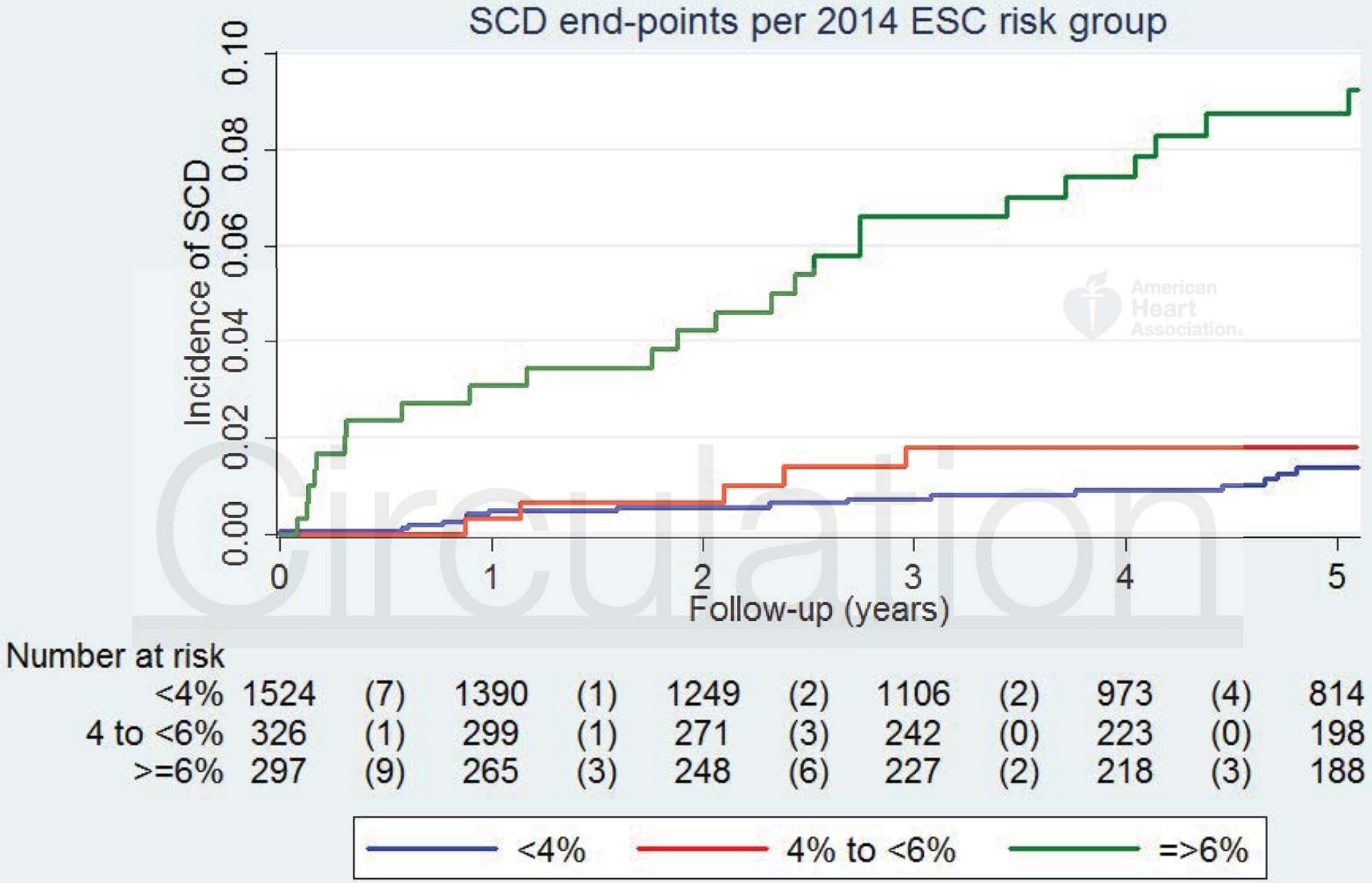
Circles represent observed and diamonds represent predicted probabilities of sudden cardiac death in 5 years using a random multiple imputation dataset. The four risk groups (1-4) were created using model-based predicted probabilities (0-2%, 2-4%, 4-6% and >6% 5-year risk of SCD). These groups are selected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



Circulation

American Heart Association®

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Circulation. published online November 30, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

TABLE 1: Participating centres

	Centre where patients were enrolled	Number of patients
1	Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA	1117
2	Academic Medical Center, Amsterdam. Heart Centre, Department of Clinical and Experimental Cardiology, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.	439
3	Centro Malattie Genetiche Cardiovascolari, Area Trapiantologica, IRCCS Fondazione Policlinico San Matteo, Piazzale Golgi 19, 27100, Pavia, Italy	384
4	The Inherited Cardiac Diseases Unit, The Heart Hospital/University College London, 16-18 Westmoreland St, London W1H 8PH, UK (part of Barts Health NHS Trust since May 2015).	372
5	Heart Failure and Inherited Cardiac Diseases Unit, Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, 1 Manuel de Falla, 28222 Majadahonda, Madrid, Spain.	338
6	Referral Centre for cardiomyopathies, Careggi University Hospital, Viale Pieraccini 1, 50134 Florence, Italy.	243
7	Department of Cardiology, Neurology and Aging science, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku-shi, post code 783- 8505, Kochi, Japan.	206
8	Heart Institute, Hadassah University Hospital. P.O.B 12000, Jerusalem, Israel IL-91120	169
9	Guy's & St Thomas' Hospital NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK.	131
10	Department of Cardiology, Odense University Hospital, Sdr. Boulevard 29 5000 Odense C, Denmark.	105
11	Inherited Cardiovascular Disease Unit, Department of Cardiology, Nicosia General Hospital, Latsia 2230, Cyprus.	104
12	Heart Muscle Disease unit, London Chest Hospital, Bonner Road, E2 9JX, UK (part of Barts Health NHS Trust since May 2015).	100
13	Columbia University Medical Center, New York Presbyterian Hospital, 173 Fort Washington Avenue, New York, NY 10032	99
14	Department of Cardiology, National Heart Centre Singapore, 5 Hospital Drive, 169609, Singapore.	95

Supplemental figure 1: The total number of HCM patients enrolled per year