Comparison of the new risk prediction model (HCM Risk-SCD) and classic risk factors for sudden death in patients with hypertrophic cardiomyopathy and defibrillator

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Aims
Hypertrophic cardiomyopathy is one of the main causes of sudden death in young people. Recent clinical practice guidelines include a risk prediction model for sudden death (HCM Risk-SCD), which facilitates the decision of whether to implant a defibrillator. The aim of our study was to ascertain the percentage of events in our series of primary prevention implantable cardioverter-defibrillator recipients with hypertrophic cardiomyopathy and whether HCM Risk-SCD predicts the onset of arrhythmic events.

Methods and results
This was an observational, retrospective cohort study, which included 48 primary prevention defibrillator recipient patients with HCM. We compiled their demographic and clinical characteristics, estimated 5-year risk using HCM Risk-SCD, and collected the documentation on arrhythmias during follow-up. The majority was male (66.7%) and mean age at implantation was 44.44 ± 14.46 years. Non-sustained ventricular tachycardia was the most prevalent risk factor (66.67%), followed by a family history of sudden death (47.92%). Mean HCM Risk-SCD was 6.15 ± 5.01%.

HCM Risk-SCD was the only factor independently associated with the onset of ventricular tachyarrhythmia, above any other classic risk factor or association [odds ratio = 1.46 (95% confidence interval 1.051–2.013); P = 0.02].

None of the 11 patients estimated as low risk using HCM Risk-SCD suffered any appropriate events (P, 0.05).

Conclusions
During an average follow-up of 4 years, 16.67% presented appropriate events (4.16%/year). HCM Risk-SCD predicted the onset of events more suitably than classic risk factors.

Keywords
Hypertrophic cardiomyopathy • Defibrillator • Sudden death

Introduction
Hypertrophic cardiomyopathy (HCM) is a heart disorder defined as a left ventricular hypertrophy ≥ 15 mm with no haemodynamic justification. It is the most frequent cardiomyopathy with a prevalence up to 1:500 individuals and is clinically associated with heart failure, sudden death, and peripheral arterial embolism. The incidence of sudden death is 0.7–1% per annum in an unselected population, and often affects young patients, for whom the decision to implantable cardioverter-defibrillator (ICD) is a complex and controversial process.

The indication for a primary prevention ICD has been based on risk criteria, many of which are qualitative and originate neither from randomized clinical trials nor from prospective studies, which casts doubt on their usefulness under certain circumstances.

Recently published European guidelines for clinical practice in HCM diagnosis and therapeutic management tackle the subject of sudden death prevention based on estimated 5-year risk using the

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HCM Risk-SCD model, which originated from a multi-centre retrospective study. This guideline uses this model to classify the risk of sudden death in three categories: low (<4%), moderate (4–6%), and high (≥6%) risk. Implantable cardioverter-defibrillator implantation may be indicated in patients at moderate risk (recommendation class IIb) and should be indicated in high-risk patients (recommendation class IIa). It is not recommended for low-risk patients.

The aim of our study was to ascertain the incidence of arrhythmic events in a series of HCM patients with primary prevention ICDs and to determine whether the new risk scale adopted in European guidelines predicts the onset of appropriate arrhythmic events in follow-up.

**Methods**

**Study observational, retroactive cohort study included 48 HCM patients with primary prevention ICDs (implanted between June 2002 and March 2014).**

Diagnosis of HCM was based on ESC criteria. We excluded patients who had already presented arrhythmic events or sudden death and those who were in a dilated phase with ventricular dysfunction. Finally, we also excluded patients with Noonan syndrome, Fabry disease, or any other storage disease or disorder of mitochondrial origin.

Implantable cardioverter-defibrillator implantation was performed in the presence of one or more risk factors for sudden death, including the classic ones: left ventricular hypertrophy ≥ 30 mm; non-sustained ventricular tachycardia (NSVT) under Holter-ECG; abnormal blood pressure response during stress test; and a family history of sudden death or prior unexplained syncope.

Demographic, clinical, and genetic characteristics were recorded along with the classic risk factors and the HCM Risk-SCD at the time of implant. The study was carried out in compliance with the 1975 Declaration of Helsinki.

**Implantation characteristics**

All implantations were transvenous, with seven dual-chamber (14.58%) and the remainder (85.42%) with single-chamber devices. Initially, the programmed therapy zone had a mean cycle length (CL) of 310.4 ± 8.2 ms; in the case of events during follow-up, device therapy programming was modified at the electrophysiologist’s discretion. In all cases, the programmed treatment was a shock (35-41J) with anti-tachycardia pacing (ATP) during charge.

**Follow-up**

Check-ups were performed by an expert electrophysiologist every 6 months in a specific visit; any events that had occurred were recorded and defined as appropriate or inappropriate, according to CL, regularity, extent/width, and morphology of the intracavitary readings.

Appropriate events were defined as an ICD intervention in response to sustained ventricular arrhythmia by means of ATP or shock.

Inappropriate events were defined as an intervention in response to supraventricular tachycardia [atrial fibrillation (AF), atrial or sinus tachycardia, etc.] or device malfunction (oversensing, electromagnetic interference, etc.)

The presence of complications related to device implantation, the onset of cardiovascular events and the necessity of admission for cardiovascular reasons were recorded in follow-up.

**Statistical analysis**

The SPSS (version 18.0) program was used for data analysis. Continuous variables are expressed as a mean ± typical deviation; categorical variables as an absolute value and a percentage. For comparison of continuous variables, Student’s t-test was used (in the case of normal distribution) or the Mann–Whitney U (for those that did not have normal distribution). Categorical variables were compared by means of contingency tables and the application of the χ²-test or Fisher’s exact test. In order to identify predictive factors, a logistic regression model was built using the variables associated with events in the non-adjusted analysis. A two-tailed value of P < 0.05 was considered to be statistically significant.

**Results**

**Baseline characteristics of the sample**

The majority was male (32, 66.7%) and mean age at implantation was 44.44 ± 14.46 years. The majority was NYHA functional classification I–II, and three patients (6.25%) were functional classification III. The majority was undergoing treatment with beta blockers (40, 83.33%), while eight patients (16.67%) were taking calcium antagonists, and six patients (12.5%) were amiodarone. Four patients (8.33%) were suffering paroxysmal/permanent AF at the time of device implantation. Twenty-seven patients underwent a genetic study to determine the presence of mutations in the genes encoding sarcomere proteins (a hypertrophic cardiomyopathy panel using ‘next generation sequencing’); 22 (81.48%) of these patients tested positive, and the most frequently affected gene was MYBPC3 (9 patients, 40.91%). Table 1 shows the general characteristics of the patients.

All of the patients had at least one risk factor for sudden death, in accordance with clinical practice guideline indications. The most frequent risk factor was the presence of NSVT in Holter-ECG (32 patients, 66.67%), followed by a family history of sudden death (23 patients, 47.92%). The average HCM Risk-SCD was 6.15 ± 5.01 and patients were reclassified into the following groups: 11 low risk (22.92%), 18 (37.5%) at moderate and 19 (39.58%) at high risk.

**Appropriate/inappropriate events**

During the average follow-up period of 4.14 ± 2.79 years, eight patients (16.67%) presented appropriate therapies with a mean CL of 267.14 ± 28.7 ms. All patients received a shock because ATP
The average time for event onset was 2.9 ± 2.71 years. There was no missing data.

In the unadjusted analysis, factors associated with an appropriate event were HCM Risk-SCD and age. There were no differences between the presence of isolated risk factors and the coexistence of two or more risk factors (Table 2). In the multivariate analysis (adjusted), HCM Risk-SCD was the only factor independently associated with the onset of appropriate events [odds ratio (OR) = 1.46 (95% confidence interval 1.051–2.013); P = 0.02] (Table 3).

As shown in Figure 1, the age is a key input. All appropriate events occurred in patients 45 years or younger at the time of device implantation.

None of the 11 low-risk patients as defined by HCM Risk-SCD, who complied with prior criteria, had events in follow-up. Of the 18 moderate risk patients, two suffered events, as did six from the high-risk group (Figure 2).

The free survival of arrhythmic events estimated by the Kaplan–Meier method showed a non-statistical significant difference between low risk and moderate/high risk (Figure 3), but it was better than the difference between one or more classical risk factors (Figure 4).

Six patients presented inappropriate events, four of which were associated with paroxysmal AF (previously in sinus rhythm) and two with sinus tachycardia. The onset of AF in follow-up was independently associated with the onset of inappropriate events with an OR of 10.46 (95% CI 1.087–100.595), P = 0.042.
The most frequent complications were electrode dislocation (two patients, 4.17%) and there was one pocket infection (2.08%) with no difference regarding the risk group that patients belonged to.

Cardiac morbidity and mortality

During the average follow-up of over 4 years, there were 10 hospital admissions, 2 for heart failure and 6 for arrhythmic events (arrhythmic storm). There were neither sudden deaths nor deaths of cardiac origin. There were no deaths for any other cause. No patients underwent heart transplant. Twelve patients presented AF episodes in follow-up, four of which provoked inappropriate therapies.

Discussion

This study shows how the use of the HCM Risk-SCD scale could help to improve the estimation of risk for sudden death in HCM patients and, therefore, a better selection of the patients who would most benefit from implantation of an ICD.

Only a small subgroup of HCM patients treated with an ICD receives potentially lifesaving shocks to terminate ventricular arrhythmias. The overall annual incidence of appropriate shocks is 4.6%. This is similar to our findings, with a high number of appropriate events (16.67% on average 4 years), indicating a high-risk profile.

The recommendation for implantation of a primary prevention ICD in HCM is not based on randomized prospective clinical trials, unlike other cardiomyopathies such as ischaemic or dilated cardiomyopathy that have a higher degree of evidence; however, the recent clinical practice guidelines and the quantitative risk estimation model (HCM Risk-SCD) try to clarify doubts that generally arise regarding these patients, and the model seems to have advantages as it provides a more exact prognosis which helps clinical decision-making. It is, therefore, a step forward from previous guidelines whose risk of sudden death algorithms was based on the simple sum of a limited number of binary clinical parameters (NSVT, severe hypertrophy, unexplained syncope, family history of SCD, and abnormal blood pressure response to exercise).

As described Christiaans et al. in a recent review, the power of some risk markers is substantially modified by age. It is included in the model HCM Risk-SCD and probably influences the best prediction of events.
In addition, use of the HCM Risk-SCD scale seems to reduce unnecessary ICD implantation, which has inherent psychological benefits and avoids the complications that accompany device implantation. The scale is also easy to use, accessible for professionals (it is available online) and gives quantitative results, which means that we are able to give more specific information to the patient.

The diagnostic yield of sarcomere gene testing in clinical cases of familial HCM is typically \( \approx 60\% \); the yield depends upon patient selection, falling to \( \approx 30\% \) in sporadic disease. We found a high percentage of positive genetic tests (81.48%), probably for a selected sample. Furthermore, it seems that a genetic condition of one or other sarcomere protein does not mark long-term prognosis, although in the case of certain high-risk mutations, implantation of an ICD would have to be individualized.

**Limitations**

One limitation is that the study population is small (48 patients) from a low-volume centre. This is a retrospective single-centre study and is therefore subject to uncontrolled bias. In addition, it only studies the risk of sudden death in ICD recipient patients, not the whole group of HCM patients under follow-up in our centre.

**Conclusions**

During an average follow-up of slightly more than 4 years, the prevalence of ventricular tachyarrhythmia treated by the device in our series of 48 patients with HCM and ICD was 16.67%.

The use of the new risk prediction model, HCM Risk-SCD, seems to facilitate better prediction of appropriate events than classic risk factors, and allows a quantitative estimation of the risk of sudden death at 5 years.

**Conflict of interest:** none declared.

**References**