Validation of the 2014 European Society of Cardiology Sudden Cardiac Death Risk Prediction Model in Hypertrophic Cardiomyopathy in a Reference Center in South America

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Sudden cardiac death (SCD) is a common cause of death in hypertrophic cardiomyopathy (HC). Our aim was to conduct an external and independent validation in South America of the 2014 European Society of Cardiology (ESC) SCD risk prediction model to identify patients requiring an implantable cardioverter defibrillator. This study included 502 consecutive patients with HC followed from March, 1993 to December, 2014. A combined end point of SCD or appropriate implantable cardioverter defibrillator therapy was assessed. For the quantitative estimation of individual 5-year SCD risk, we used the formula: $1 - 0.998^{\exp(\text{Prognostic index})}$. Our database also included the abnormal blood pressure response to exercise as a risk marker. We analyzed the 3 categories of 5-year risk proposed by the ESC: low risk (LR) <4%; intermediate risk (IR) ≥4% to <6%, and high risk (HR) ≥6%. The LR group included 387 patients (77%); the IR group 39 (8%); and the HR group 76 (15%). Fourteen patients (3%) had SCD/appropriate implantable cardioverter defibrillator therapy (LR: 0%; IR: 2 of 39 [5%]; and HR: 12 of 76 [16%]). In a receiver-operating characteristic curve, the new model proved to be an excellent predictor because the area under the curve for the estimated risk is 0.925 (statistical C: 0.925; 95% CI 0.8884 to 0.9539, p <0.0001). In conclusion, the SCD risk prediction model in HC proposed by the 2014 ESC guidelines was validated in our population and represents an improvement compared with previous approaches. A larger multicenter, independent and external validation of the model with long-term follow-up would be advisable. **(Am J Cardiol 2016;■:■−■)**

The identification of patients with hypertrophic cardiomyopathy (HC) who are at risk of sudden cardiac death (SCD) is one of the biggest challenges cardiologists face. Although considerable progress has been made in this field, identifying patients at high risk (HR) is still a very complex issue, given that HC is caused by different etiologies, has different forms of presentation and expression, the pathophysiological mechanisms are very complex, and prevalence of SCD is relatively low. In recent years, risk stratification has been based on the recommendations of the 2003 expert guidelines of the American College of Cardiology/European Society of Cardiology (ACC/ESC), and the 2011 guidelines of the ACC Foundation/American Heart Association (ACCF/AHA), which proposed at least 5 major risk predictors assessed noninvasively and accepted as such based on observational studies and retrospective cohorts: (1) a family history of SCD, (2) unexplained syncope, (3) the presence of nonsustained ventricular tachycardia on Holter monitoring, (4) evidence of extreme ventricular hypertrophy (especially with a thickness ≥30 mm), and (5) abnormal blood pressure response to exercise (ABPRE) in young patients.[1,2] However, a validation of the 2003 and 2011 guidelines has shown that they have limited power to distinguish between patients at HR and low risk (LR).[3] This motivated O'Mahony et al[4] to develop a new mathematical and statistical model for predicting risk of SCD (HC risk-SCD) that allows for an individual quantitative estimate of the risk of SCD at 5 years. This model was included in the 2014 guidelines for diagnosis and management of HC of the ESC.[5] The purpose of this study was to validate the power of the 2014 ESC SCD risk prediction model in HC (HC risk-SCD) in a population of South America to identify patients who could benefit from implantable cardioverter defibrillator (ICD) implantation for primary prevention of SCD.

Methods

This retrospective observational study included 502 consecutive patients with HC at the Favaloro Foundation University Hospital, Buenos Aires, Argentina, from March 1993 to December 2014. The diagnosis of HC was based on

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the echocardiographic demonstration of an unexplained increase in wall thickness ≥15 mm, in the absence of abnormal load conditions.[1–5] The follow-up was conducted by clinical consultations, review of medical records, and telephone interviews. Patients who met certain characteristics that were not validated on the original study of O'Mahony et al[4] were excluded: patients treated with surgical myectomy, alcohol septal ablation, heart transplant, patients younger than 16 years old, and with metabolic diseases/or syndromes (e.g., Noonan syndrome and Fabry's disease), HC treated with an ICD for secondary prevention of SCD, and patients with <5 years of follow-up, or who were lost to follow-up.

For the quantitative estimation of the individual risk of SCD at 5 years, we used the HC risk-SCD formula:

$$\text{Probability SCD at 5 years} = 1 - 0.998^{\exp(\text{Prognostic index})} \times 100$$

where prognostic index = (0.15939858 × maximal wall thickness [mm]) − (0.00294271 × maximal wall thickness^2 [mm^2]) + (0.0259082 × left atrial diameter [mm]) + (0.00446131 × maximal [rest/Valsalva] left ventricular outflow tract gradient [mm Hg]) + (0.4583082 × family history SCD) + (0.82639195 × nonsustained ventricular tachycardia) + (0.71650361 × unexplained syncope) − (0.01799934 × age at clinical evaluation [years]).[4,5]

We analyzed the 3 categories of 5-year risk proposed by the 2014 ESC guidelines on diagnosis and management of HC: LR <4% (ICD generally not indicated), intermediate risk (IR) ≥4% to <6% (ICD may be considered), and high risk (HR) ≥6% (ICD should be considered).[5]

The primary end point was a composite of SCD or appropriate ICD shock (considered as equivalent to SCD), identical to the end point described by O'Mahony et al in the original study (HC Risk-SCD).[4] As in other studies, SCD was defined as instant and unexpected death occurring within the first hour of the onset of symptoms in an individual who was otherwise in a stable condition or patients resuscitated after cardiac arrest. Appropriate ICD shock for ICD was defined in agreement with previous studies, such as those interventions for ventricular fibrillation or fast ventricular tachycardia (>200 beats/min).[4,6]

All statistical analyses were performed using SPSS, version 21 (IBM Corp, Chicago, Illinois). Continuous variables were expressed as means ± SD, and comparison between groups was performed using the Mann−Whitney test. The noncontinuous variables were expressed as counting number (percent of total) and compared using the chi-square test or Fisher's exact test as corresponding. Follow-up time for each patient was calculated from the date of their first assessment to date in the study end point, death for other causes, or until the date of its most recent assessment. The annual event rate was calculated by dividing the number of patients reaching the end point during the whole follow-up period for that end point. The cumulative probability of the occurrence of an outcome was estimated using the Kaplan−Meier method. To discriminate the performance of the new risk stratification model together with the others based on the observation of conventional risk factors, receiver-operating characteristic (ROC) curves plotting sensitivity as a function of 1-specificity were performed. From them the value of area under the curve (C statistic) was established, where values near 0.5 indicate little or no predictive value and values close to 1 indicate an excellent predictive value.

Table 1
Baseline clinical characteristics of the 502 patients

Variable	SCD/AT		p Value
	No (n = 488)	Yes (n = 14)	
Age (years)	52±18	43±21	<0.001
Males	308 (63%)	7 (50%)	NS
Maximum wall thickness (mm)	22±5.8	23.2±7.2	NS
Left atrial diameter (mm)	45.8±7.8	44.6±8.4	NS
Maximum LVOT gradient (mmHg)	76±53	48.4±48	NS
Atrial fibrillation	75 (16%)	2 (14%)	NS
Risk factors			
Family history of SCD	47 (10%)	5 (36%)	0.010
Non-sustained ventricular tachycardia	53 (11%)	5 (38%)	0.016
Wall thickness ≥ 30 mm	65 (14%)	6 (43%)	0.008
Unexplained syncope	42 (9%)	3 (21%)	NS
Abnormal blood pressure response to exercise	14 (3%)	6 (43%)	<0.001
Number of risk factors			
0	348 (71%)	4 (29%)	0.001
1	76 (16%)	1 (7%)	NS
≥ 2	64 (13%)	9 (64%)	<0.001
HC risk-SCD (%)	3.2 (3%)	8.5 (3%)	<0.001

Categorical data are presented as actual count (percentage). Continuous data are presented as mean ± SD.

Results

Out of a total of 798 patients with HC, the study population included 502 (63%); aged 51 ± 18 years, 62% men. Baseline characteristics of the study population are reported in Table 1.

Of the 502 patients who met the inclusion criteria, 387 (77%) had LR; 39 (8%) IR; and 76 (15%) HR. The ICDs for primary prevention of SCD were implanted in 96 (19%) of the 502 patients (in LR category were implanted 6 ICD [1%]; IR: 24 [5%]; and HR: 66 [13%]). A total of 188 patients (37%) presented a basal gradient ≥30 mm Hg; 79 (16%) patients presented atrial fibrillation.

The mean of follow-up in the whole group was 8.58 ± 4.28 years. Fourteen (3%) had the end point of SCD/appropriate implantable cardioverter defibrillator therapy (AT) within 5 years of follow-up (in the LR category: 0%; IR: 2 of 39 [5%]; and HR: 12 of 76 [16%]), of which 4 occurred during the first year of follow-up. Of the 14 patients, 6 (43%) had SCD and 8 (57%) had AT. Note that the 2 patients who received AT in the IR group were younger than 40 years old and had ABPRE (Figure 1).

In Figure 2, the ROC curve shows that the HC risk-SCD was an excellent predictor because the area under the curve for the calculated risk was 0.925 (C statistic of 0.925; 95% CI 0.8884 to 0.9539, p <0.0001). Figure 2 shows ROC curves for the criteria of the 2003 ACC/ESC, 2011 ACCF/AHA, and the 2014 ESC guidelines for 2 cut-off levels of 4% and 6% with increasing prediction values