









ICD indication in hypertrophic cardiomyopathy: which algorithm to use?

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SUMMARY

OBJECTIVE: This study aimed to evaluate the agreement in the indication of implantable cardioverter-defibrillators in patients with Hypertrophic cardiomyopathy, as per the 2014 European Society of Cardiology and 2020 American Heart Association recommendations, and evaluate fragmented QRS as a predictor of cardiovascular outcome.

METHODS: Retrospective cohort with 81 patients was evaluated between 2019 and 2021. Patients with hypertrophic cardiomyopathy ≥ 16 years old were included. Exclusion criteria include secondary myocardopathy and follow-up < 1 year. Kappa coefficient was used to determine the agreement. Survival and incidence curves were determined by Kaplan-Meier method. A $p < 0.05$ was considered significant.

RESULTS: The fragmented QRS was identified in 44.4% of patients. There were no differences between patients with and without fragmented QRS regarding clinical parameters, echocardiography, fibrosis, and sudden cardiac death risk. During follow-up of 4.8 ± 3.4 years, there was no sudden cardiac death, but 20.6% patients with implantable cardioverter-defibrillator had at least one appropriate shock. Three of the seven appropriate shocks occurred in European Society of Cardiology low- to moderate-risk patients. Three shocks occurred in moderate-risk patients and four in American Heart Association high-risk patients. Overall recommendations agreement was 64% with a kappa of 0.270 ($p = 0.007$). C-statistic showed no differences regarding the incidence of appropriate shock ($p = 0.644$).

CONCLUSION: sudden cardiac death risk stratification algorithms present discrepancies in implantable cardioverter-defibrillator indication, both with low accuracy.

KEYWORDS: Sudden cardiac death. Hypertrophic cardiomyopathy. Implantable cardioverter-defibrillator. Cardiac arrhythmia.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with an estimated prevalence of 1–167 individuals¹. It is recognized as the main cause of sudden death (SD) in young people². It is commonly asymptomatic. When present, the main symptoms are chest pain, dyspnea, palpitation, and syncope³.

Through risk stratification strategies and prophylactic implantable cardioverter-defibrillator (ICD) indication, the mortality of patients with HCM has been reducing from 6 to $< 1\%$ per year^{1,4}. However, recommendations for implantation of ICD are divergent and tend to over- or underestimate the real risk of SD, increasing the risk of unnecessary intervention in low-risk patients or nonindication in high-risk patients^{1,4,5}.

Traditionally, the main risk factors for MS are age, report of syncope, family history of multiple sclerosis (MS), evidence of ventricular arrhythmia, and left ventricular hypertrophy (LVH) ≥ 30 mm^{4,6}. Although widely validated, these parameters have low accuracy in predicting MS in low- and medium-risk patients, which correspond to the majority of patients with HCM⁷.

Some studies have shown that fragmented QRS (fQRS) on electrocardiogram (ECG) correlates with myocardial fibrosis and represents a potential precursor of heart failure (HF) and arrhythmic events⁷. Despite this, the relevance of the fQRS in HCM is limited and its role in the prediction of SD is controversial⁸.

The aim of this study was to evaluate the agreement in the indication of ICD as primary prophylaxis of SD in HCM patients, according to the 2014 European Society of Cardiology (ESC) and

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2020 American Heart Association (AHA) recommendations, and to evaluate the fQRS as a predictor of cardiovascular outcome.

METHODS

Type of study and population

This is a retrospective cohort study carried out in a university cardiology outpatient clinic specialized in HCM.

Inclusion criteria were diagnosis of HCM and age ≥ 16 years, while exclusion criteria were indication of ICD as secondary prophylaxis, follow-up time < 1 year, and incomplete medical records.

The clinical variables collected were age, sex, clinical data (family history of SD, symptoms, ICD implantation), data from complementary examinations (ECG, transthoracic echocardiogram [ECOTT], cardiac magnetic resonance [CMR], 24 h Holter), clinical outcomes, and follow-up time.

The diagnosis of HCM was defined as LVH ≥ 15 mm in the largest segment (or ≥ 13 mm in those with a family history of HCM) in the absence of cardiac or systemic diseases that would justify ventricular overload⁴.

The definition of SD was any sudden-witnessed death with or without documented ventricular fibrillation (VF), death within 1 h of the onset of new symptoms, or nocturnal deaths without prior history of worsening symptoms⁹. Time of follow-up was determined by the difference in years between the initial assessment and the last visit or outcome. The functional class was determined by the New York Heart Association (NYHA).

In the case of shock administration by the ICD, the electrograms recorded by the device were retrieved and analyzed. Shocks were considered appropriate in the event of sustained VT and VF¹⁰.

The primary end point was the composite of SD or equivalent SD (SDE), namely, aborted MS and/or appropriate ICD shock. The secondary end point, acronym SEHS, was composed of SDE, hospitalization for decompensated HF, and fatal or nonfatal stroke.

The techniques used to perform the ECOTT and CMR were described previously¹¹.

Electrocardiographic analysis

The duration of QRS complex was manually determined in long lead II. In patients with narrow QRS (< 120 ms), fQRS was defined as the presence of an additional R wave or notch in the R or S wave; in the case of wide QRS (≥ 120 ms), 2 notches or higher of R or S were considered¹².

Risk stratification for cdi implantation

The probability of MS in 5 years was calculated using the mathematical model validated by the ESC⁴.

Each patient had its indication for ICD determined according to the recommendations of each guideline, grouped according to the level of clinical evidence:

- ESC 2014⁴ – using estimated risk (ER) of SD in 5 years
 - Class IIa – ER $\geq 6\%$
 - Class IIb – ER < 6 and $\geq 4\%$
 - Class III – ER $< 4\%$
- AHA 2020¹
 - Class IIa – at least one of the following: family history of MS, maximal LVH ≥ 30 mm, unexplained syncope; apical aneurysm; left ventricular ejection fraction (LVEF) $\leq 50\%$
 - Class IIb – nonsustained ventricular tachycardia (NSVT) or myocardial fibrosis on CMR $\geq 15\%$
 - Class III – absence of the aforementioned factors

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or as median and range of 25th and 75th quartiles, as appropriate, and categorical variables as absolute and proportional values. The Shapiro-Wilk test was used to determine normality.

Unpaired Student's t-test or Mann-Whitney U test was used in the analysis of continuous variables, while the χ^2 test or Fisher's exact test was used for categorical variables.

Survival curves, together with the p-value of the log-rank test, were calculated using the Kaplan-Meier method. The analysis was adjusted for age, sex, family history of MS, NYHA (I–II vs. III–IV), maximal LVH, gradient in left ventricular outflow tract (LVOT), syncope, and the presence of VT or NSVT on 24 h Holter. Receiver operating characteristics curve (ROC), area under the curve (AUC), and Harrell C-statistics analyses were used to assess the accuracy of the guidelines for predicting appropriate ICD shock. The linearly weighted kappa coefficient was calculated to determine the degree of agreement between the recommendations of the 2014 ESC and 2020 AHA 2020. For all the analyses, $p < 0.05$ was considered significant.

Ethical aspects

The study was submitted and approved by the Research Ethics Committee. All Brazilian legal norms and Helsinki Declaration principles were observed. Since it was a retrospective study, the collection of the informed consent form was waived.

RESULTS

From March 2019 to February 2021, 96 patients with HCM were identified, of which 15 were excluded from the study

due to not meeting the established criteria; therefore, only 81 patients were included in the study.

The fQRS was diagnosed in 36 (44.4%) patients. There was no statistically significant difference between patients with and without fQRS regarding clinical, echocardiographic, fibrosis, and estimated risk of MS (Table 1).

During a mean follow-up of 4.8 ± 3.4 years, no SD occurred, but 7 (20.6%) of 34 patients with ICD had at least one appropriate shock, 4 (4.9%) hospitalizations for decompensated HF, and 6 (7.4%) nonfatal cerebrovascular events. Three of the seven appropriate shocks occurred in patients considered to be at low or moderate risk by the 2014 ESC guidelines. In the case of the

2020 AHA guidelines, three of the appropriate shocks occurred in patients at moderate risk and four shocks in patients at high risk. The incidence of SDE was 10.2% and that of SEHS was 21.6%.

The agreement between the indications for ICD implantation according to the 2014 ESC and 2020 AHA guidelines was 64% ($\kappa = 0.270$; $p = 0.007$) (Table 2).

The Kaplan-Meier curve showed a trend toward lower outcome-free survival in patients with fQRS (71.3 vs. 82.6%; $p = 0.515$, Figure 1A). There was no statistical difference regarding the cumulative incidence of appropriate shock (10.5 vs. 16%, with and without fQRS; $p = 0.598$, Figure 1B).

Considering the indications for ICD implantation as a binary outcome (implant [evidence IIa/IIb] or not implant [evidence III]), C-statistics analysis did not show differences regarding the incidence of appropriate shock ($p = 0.644$). The AUC was 0.557 for the 2014 ESC recommendations (95%CI 0.406–0.707) and 0.548 for the 2020 AHA (95%CI 0.548–0.636) Figure 2.

Table 1. Basic characteristics of the study population.

	fragmented QRS (n=36)	No fragmented QRS (n=45)	p-value
Age, years	42.8±15.6	48.1±15.8	0.137 ^a
Gender male	17 (47.2)	23 (51.1)	0.728 ^b
SD family history	21 (58.3)	23 (51.1)	0.564 ^b
NYHA III/IV	3 (8.3)	2 (4.4)	0.470 ^c
Syncope history	13 (36.1)	19 (42.2)	0.168 ^b
ICD implant	14 (38.9%)	20 (44.5)	0.615 ^b
TTE			
LVEF (%)	67 (62–72)	69 (63–74)	0.284 ^d
Max LVH (mm)	20 (16.5–27.6)	20 (17–24)	0.668 ^d
LA (mm)	39 (34–46)	39 (38–44)	0.647 ^d
LVOT (mmHg)	0 (0–31)	0 (0–30)	0.668 ^d
Myocardial fibrosis (%) ⁿ	3.5 (2.3–7.5)	3.5 (1.7–13.8)	0.542 ^d
ECG			
AFib	3 (8.3)	6 (13.3)	0.724 ^c
LVH	18 (50.0)	17 (37.8)	0.399 ^d
LAO	10 (27.8)	9 (20.0)	0.515 ^d
Stroke/TIA	2 (5.6)	6 (13.3)	0.284 ^c
SD risk in 5 years (%)	4.6 (2.7–7.3)	3.8 (2.1–6.1)	0.541 ^d

Values expressed as n (%), mean±standard deviation, or median (p25–75%). SD: sudden death; NYHA: New York Heart Association functional class; ICD: implantable cardioverter-defibrillator; TTE: transthoracic echocardiogram; LVEF: left ventricular ejection fraction; Max LVH: maximal left ventricular hypertrophy; LA: left atrium; LVOT: left ventricular outflow tract; AF: atrial fibrillation; LVH: left ventricular hypertrophy; LAO: left atrial overload; Stroke/TIA: stroke or transient ischemic stroke.

ⁿOnly 55 (67.9%) patients underwent CMR; ^aStudent's t-test; ^b χ^2 test; ^cFisher's exact test; ^dMann-Whitney U test.

DISCUSSION

In this study, we evaluated the agreement between the 2014 ESC and 2020 AHA guidelines in the indication of ICD as primary prophylaxis of MS in patients with HCM. Our results show significant divergence in the indication of ICD, with an overall agreement of 64%. The 2020 AHA algorithm indicated class IIa ICD in 69% of patients, compared to 40.7% by 2014 ESC. Two patients classified as low risk by ESC had appropriate shocks 1 and 5 years after ICD implantation. Of the 13 patients classified by the AHA as low risk, there was a divergence from the ESC in only one case.

The analysis of the agreement of indications resulted in a kappa of 0.270. Kappa coefficient between 0.21 and 0.39 represents minimal agreement, implying that only 4–15% of the indications analyzed between both guidelines are, in fact, reliable¹³.

Mattos et al. demonstrated that in relation to the 2011 AHA, the ESC algorithm also had low agreement and would

Table 2. Implantable cardioverter-defibrillator indication agreement according to the degree of evidence.

AHA 2020	ESC 2014		
	III	IIb	IIa
III	12	0	1
IIb	w6	1	5
IIa	16	13	27

General agreement: 64.2%, $\kappa = 0.270$ (95%CI 0.118–0.422; $p = 0.003$) ESC: European Society of Cardiology; AHA: American Heart Association. IIa, IIb, III: degrees of scientific evidence for implantable cardioverter-defibrillator; implantation according to each guideline.

leave all patients (8/90) unprotected with appropriate shock⁵. Other studies have also demonstrated low sensitivity of the algorithm, especially in patients considered to be at low risk^{14,15}. Our results showed low accuracy of the algorithm to predict MS, especially in the group considered low risk.

The 2020 AHA recommendations showed high sensitivity (100%), but their low specificity (17.6%) implies unnecessary indication of ICD in low-risk patients. ICD implantation is related to complications such as infection and inappropriate shocks, with an incidence of 2.1% per year¹⁶. In the C-statistics analysis, both guidelines showed similar discrimination in predicting appropriate shock.

In HCM studies, a good correlation has been shown between the presence of fQRS and fibrosis estimated by CMR and histology¹⁷. In our sample, it was not possible to demonstrate the association between fQRS and fibrosis. There was a trend toward a greater outcome-free survival in patients without fQRS, but this difference was not significant. There was no statistical difference between the cumulative incidence of appropriate shocks between patients with or without fQRS, despite a trend toward more shocks in the fQRS group (10 vs. 16%).

Few studies have evaluated the direct link between MS risk and appropriate ICD shock in patients with HCM and the presence of fQRS. One study evaluated the calculated risk of SD in 5 years of the 2014 ESC and showed that the presence of fQRS was related to a risk of SD >4%¹⁸. In the SHIFT study, the fQRS was included as a risk predictor with a hazard ratio of 3.6⁷. However, the study included only patients at low and moderate risk for MS, compromising its practical applicability.

The spectrum of clinical presentation of HCM is quite heterogeneous. The mechanisms underlying the occurrence

of fibrosis and arrhythmia are not fully understood and appear to be influenced by epigenetic factors¹⁹. Rigid predictor models are unable to represent the complexity of individual risk, which reinforces the role of specialist experience in risk stratification and individualized indication of primary ICD prophylaxis.

Some limitations of this study were the sample size, the retrospective design, and the factor of being unicentric. The occurrence of appropriate shocks would not necessarily represent

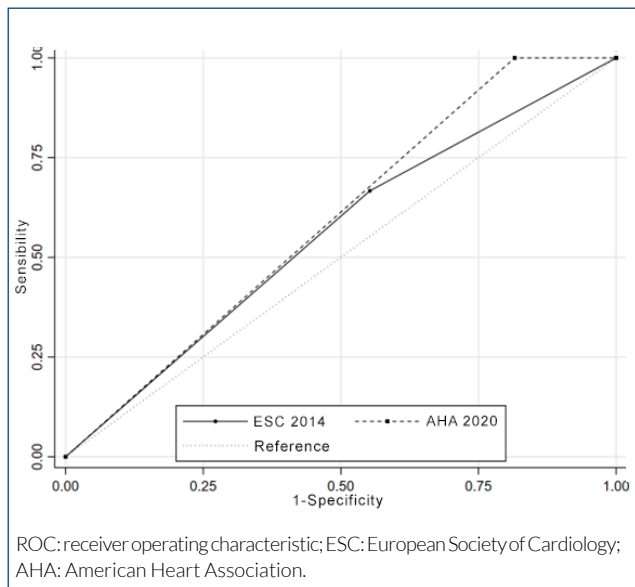


Figure 2. Receiver operating characteristic curve comparing the incidence of appropriate shocks according to European Society of Cardiology 2014 and American Heart Association 2020 guidelines implantable cardioverter-defibrillator indication.

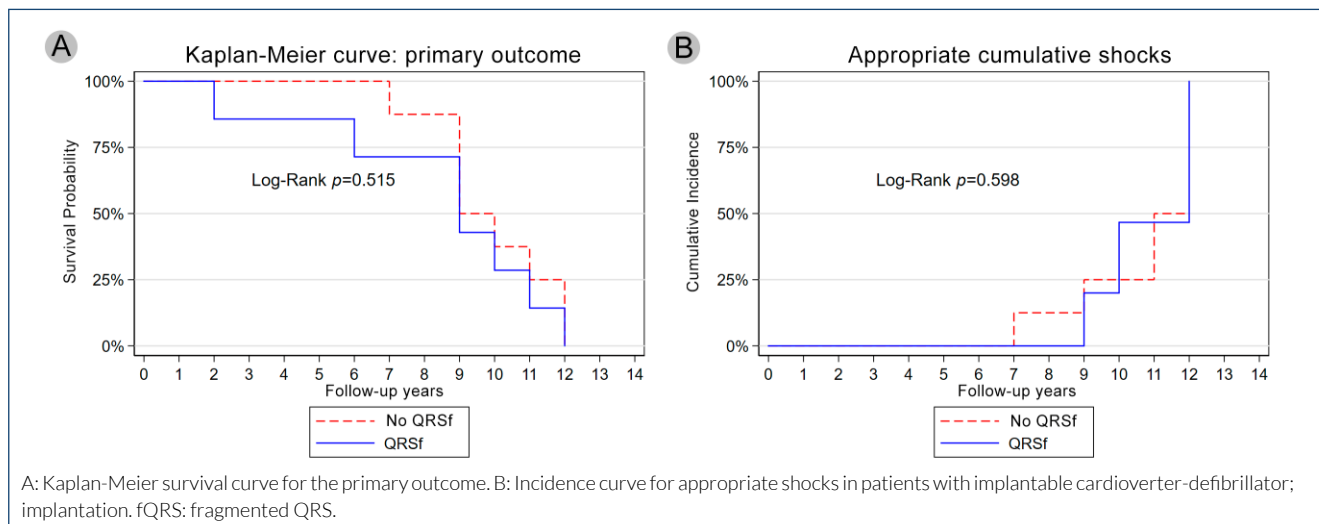


Figure 1. Survival and incidence curves for the primary outcome and appropriate shocks.

life-threatening events and the patients treated tended to present later diagnoses and greater severity.

CONCLUSIONS

The 2014 ESC and 2020 AHA MS risk stratification algorithms for HCM patients present discrepancies in the indication of ICD implantation, both with low accuracy. The European guideline showed better specificity, while the American guideline showed excellent sensitivity, despite similar discrimination using C-statistics.

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