Prediction of sudden death risk in obstructive hypertrophic cardiomyopathy: Potential for refinement of current criteria

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ABSTRACT

Background: In patients with hypertrophic cardiomyopathy (HCM), the use of an implantable cardioverter defibrillator (ICD) can prevent sudden cardiac death (SCD). In patients with obstructive HCM, we sought to determine the prognostic utility of European Society of Cardiology (ESC) SCD risk score and to evaluate whether additional factors modulate SCD risk.

Methods: We studied 1809 consecutive patients with obstructive HCM (mean age, 50 ± 14 years; 63% males; mean maximal outflow tract gradient, 93 ± 40 mm Hg). Major SCD risk factors were recorded (0, 1, or ≥ 2) and % 5-year ESC SCD risk score was calculated. The need for surgical myectomy and a composite endpoint (SCD and/or appropriate ICD discharge) were recorded.

Results: The distribution of major SCD risk factors was 0 in 65% of the patients, 1 in 26%, and ≥ 2 in 8%. The 5-year ESC risk was low ($<4\%$) in 65% of the patients, intermediate (4%-6%) in 18%, and high ($>6\%$) in 17%. Surgery was performed in 1160 patients (64%), and 361 (20%) had AF. At a mean of 8.8 ± 4 years, 169 patients had a composite event (154 SCDs). At 5 years, despite a wide range of expected events (2.5%-9%), the observed events ranged from 4.6% to 5% across 3 SCD risk categories (Hosmer–Lemeshow $P = .32$). On multivariable competing-risk analysis, myectomy (subdistribution hazard ratio [sHR], 0.69; 95% confidence interval [CI], 0.47-0.83) was associated with lower risk of longer-term composite events ($P < .01$), whereas ESC SCD risk score was not (sHR, 1.31; 95% CI, 0.75-2.25; $P = .36$).

Conclusions: In patients with obstructive HCM, despite a wide range of expected 5-year primary event rate, the observed primary events were similar across the 3 ESC SCD risk categories, with myectomy mitigating SCD risk. In patients with obstructive HCM, SCD risk may need to be refined for patients following myectomy. (J Thorac Cardiovasc Surg 2018;156:750-9)

Five-year expected versus observed composite events in the entire study sample.

Central Message

In a study of 1809 patients with obstructive hypertrophic cardiomyopathy (HCM), despite a wide range of expected 5-year primary event rates (2.5%-9%), the observed primary events were similar ($\sim 5\%$) across the 3 ESC SCD risk categories, with myectomy mitigating SCD risk. In patients with obstructive HCM, SCD risk stratification may need to be refined for patients following myectomy.

Perspective

In a large group of adults with obstructive hypertrophic cardiomyopathy (HCM), despite a wide range of expected 5-year event rates, the observed events were similar across different SCD risk categories. The addition of atrial fibrillation and myectomy to the SCD risk score significantly reclassified risk, along with providing incremental prognostic utility.

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Hypertrophic cardiomyopathy (HCM) is a commonly inherited cardiomyopathy with a varied phenotypic expression, and sudden cardiac death (SCD) is a devastating

but potentially avoidable complication.^{1,2} With increased awareness and improvement in diagnostic and therapeutic strategies, including the use of implantable cardioverter defibrillators (ICDs) in selected high-risk patients, the rate

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Scanning this QR code will take you to supplemental tables, video, and appendix for this article.

Abbreviations and Acronyms

AF	= atrial fibrillation
CHF	= congestive heart failure
CI	= confidence interval
ESC	= European Society of Cardiology
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter defibrillator
IQR	= interquartile range
LV	= left ventricular
LVOT	= left ventricular outflow tract
NYHA	= New York Heart Association
SCD	= sudden cardiac death
sHR	= subdistribution hazard ratio
VT	= ventricular tachycardia

of SCD has been reduced considerably, to 0.5%/year.^{1,2} The recommendation for an ICD has been based on identifying high-risk individuals using a combination of traditional SCD risk factors, as recommended by American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.^{1,2} However, recent reports have suggested that this approach is sensitive but not very specific, with limited discriminative power.³

Based on that argument, a novel risk prediction score that provides an individualized 5-year SCD risk was developed and subsequently incorporated into European Society of Cardiology (ESC) guidelines and validated in a different population.^{2,4} However, the ESC SCD risk score remains controversial, with a recent countersuggestion that it might potentially misclassify risk.⁵ Moreover, it is not entirely clear how the risk model will perform in different populations with significantly different management strategies.

It is well established that an important consideration in HCM is identifying concomitant left ventricular (LV) outflow tract (LVOT) obstruction, which, when evaluated diligently, is present in ~70% of cases.⁶ Although previous SCD risk models have not considered the potential of surgical relief of LVOT obstruction to modulate outcomes, this relief has been associated with improved outcomes (including cardiac death and appropriate ICD therapy) compared with no surgery.^{7,8} In fact, in the cohort on which the recent 2014 ESC guidelines were based, LVOT obstruction was not uniformly present in all patients, and surgical relief of LVOT obstruction was performed in only a very small proportion of patients.² Thus, in a large group of patients with obstructive HCM who were evaluated at our high-volume tertiary care HCM center, we sought to evaluate the independent prognostic utility provided by the ACC/AHA and ESC SCD risk scores and to determine whether additional factors, such as myectomy, help modulate SCD risk.

METHODS**Study Sample**

The observational study sample comprised 1809 consecutive patients age ≥ 18 years with documented obstructive HCM who underwent a clinical evaluation at our tertiary care center between 1997 and 2013. These patients constitute a part of an ongoing Institutional Review Board–approved registry with a waiver of individual informed consent. We excluded patients with concomitant moderate or greater aortic/mitral stenosis on initial echocardiography ($n = 162$), patients with LV ejection fraction $< 50\%$ ($n = 38$), patients with maximal (including provokable) LVOT obstruction < 30 mm Hg ($n = 407$), patients with an apical HCM variant ($n = 62$), and patients at high risk who underwent alcohol septal ablation after being turned down for surgery due to prohibitive noncardiac comorbidities⁹ ($n = 135$).

The diagnosis of HCM was made by experienced cardiologists based on typical features, with ventricular myocardial hypertrophy (LV wall thickness ≥ 15 mm) in the absence of any other disease responsible for hypertrophy.^{1,2} In addition, in patients with borderline LV wall thickness (~ 15 mm), the presence of resting/provocable LVOT obstruction (LVOT gradient ≥ 30 mm Hg), likely due to concomitant papillary muscle/mitral valve abnormalities, also aided the diagnosis.^{1,2} No patient had uncontrolled hypertension or the characteristic sigmoid-shaped septum with dynamic LVOT obstruction commonly observed on echocardiography with hypertensive heart disease.^{10,11}

Baseline (including ACC/AHA SCD risk factors¹) and follow-up data were entered prospectively into the electronic medical record at the time of the initial visit and subsequently extracted manually. A history of nonsustained ventricular tachycardia (VT; defined as wide complex tachycardia at ≥ 120 bpm, lasting > 3 beats but < 30 seconds, or sustained VT lasting > 30 seconds) and atrial fibrillation (AF) were recorded, based on history, electrocardiography, Holter monitoring, and telemetry reviews in all patients.

Imaging

All patients underwent comprehensive echocardiography evaluation using commercially available equipment (Philips, Andover, Mass; GE Healthcare, Little Chalfont, UK; and Siemens Healthcare, Malvern, Pa). Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines.¹² Resting LVOT peak velocity was measured by continuous-wave Doppler echocardiography, and pressure gradient was estimated using a simplified Bernoulli equation. Care was taken to avoid contamination of the LVOT waveform by mitral regurgitation if present. In patients with a resting LVOT gradient < 30 mm Hg, provocative maneuvers, including Valsalva and amyl nitrite, were used. In patients with a low resting LVOT gradient and/or New York Heart Association (NYHA) class I or II symptoms, we performed exercise treadmill echocardiography to assess exercise impairment, blood pressure response, and maximal postexercise LVOT gradient.^{13,14} Abnormal blood pressure response, defined as a 20-mm Hg drop in systolic blood pressure at peak stress or lack of augmentation at peak stress, was recorded.^{1,2} In patients with a resting peak LVOT gradient > 100 mm Hg, provocative maneuvers were not performed. The degree of resting mitral regurgitation was assessed (none to severe) using multiple criteria.¹⁵ Grades of resting diastolic function were assigned, based on multiple criteria (ie, E:A ratio, deceleration time, left atrial area, and LV ejection fraction).¹⁶ Tissue Doppler data were incorporated where available in the original imaging. Missing data were manually collected from stored images.

Calculation of SCD Risk

We recorded major ACC/AHA SCD risk factors (0, 1, or ≥ 2), along with disease modifiers, as described previously.¹ Nonsustained VT and abnormal blood pressure response to exercise (with severe LVOT obstruction) were not considered major risk factors, according to the most recent guidelines.¹ In addition, based on the 2014 European guidelines, we calculated a 5-year risk of SCD using the following formula:² $1 - 0.998^{(\text{prognostic index})}$. The prognostic index was calculated

as $0.15939858 \times \text{maximal wall thickness (mm)} + 0.00294271 \times \text{maximal wall thickness}^2 \text{ (mm}^2\text{)} + 0.0259082 \times \text{left atrial diameter (mm)} + 0.00446131 \times \text{maximal LVOT gradient (mm Hg)} + 0.4583082 \times \text{family history of SCD} + 0.82639195 \times \text{nonsustained VT} + 0.71650361 \times \text{unexplained syncope} + 20.01799934 \times \text{age at clinical evaluation (years)}$. The maximal LVOT gradient was recorded as the highest number obtained either at rest or provocation (but excluding the maximal gradient obtained on exercise stress echocardiography).³

Surgery for LVOT Obstruction

In patients who had undergone surgery to relieve LVOT obstruction, the date and type of surgical procedures performed were recorded: myectomy, myectomy + mitral valve repair/replacement, myectomy + coronary artery bypass grafting, and myectomy with or without coronary artery bypass grafting with or without valve surgery. We have described our surgical techniques in detail previously.¹⁷⁻¹⁹ Indications for surgery were as follows: NYHA class III/IV or intractable angina, exertional syncope with severe (>50 mm Hg) LVOT obstruction, and impaired exercise capacity. Patients deemed in NYHA class I had additional reasons (ie, exertional syncope with severe LVOT obstruction or impaired exercise capacity) to undergo surgery. The need for surgery was ascertained after a consensus between experienced cardiologists and cardiothoracic surgeons.

Outcomes Assessment

The duration of follow-up ranged between initial office visit to event/last office follow-up. We ascertained events by phone call follow-up to the patient or a family member. Death notification was confirmed by observation of a death certificate or verified with a family member. When telephone follow-up was not feasible, we queried state and nationally available databases. The last query was performed in May 2016. Based on a review of records and/or discussion with family members, the cause of death was classified as cardiac death, noncardiac death, or unknown. Cardiac death was further characterized as either due to SCD or related to congestive heart failure (CHF). SCD was defined as unexpected sudden collapse occurring <1 hour after symptom onset in otherwise stable patients.²⁰ In addition, we recorded successful resuscitation from cardiac arrest or appropriate ICD shocks (with a defibrillation threshold of >200 bpm on electrogram reviews).²⁰ For the primary composite endpoint, we included SCD and appropriate ICD discharge. Patients with an unknown cause of death were included as part of the composite primary outcome, because these patients died suddenly and there were no documented noncardiac comorbidity/chronic illness (including CHF) to explain their death, as described previously.²¹ We also recorded a secondary outcome of all-cause mortality and appropriate ICD discharge. In addition, the presence and etiology of stroke (transient or permanent) was recorded based on clinical neurologic evaluation and appropriate neuroimaging. Arrhythmias, occurring during follow-up (AF, VT, and nonsustained VT) were recorded based on history, electrocardiography, Holter monitoring, and telemetry performed at our institution or locally during follow-up. In the subgroup that underwent surgery, AF occurring within the first 30 days postoperatively was not included in the analysis.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation and/or median with interquartile range (IQR) and compared using analysis of variance (for normally distributed data) or the Mann-Whitney *U* test (for nonnormally distributed data), as appropriate. Categorical data are expressed as count and percentage and compared using the χ^2 test. Hosmer-Lemeshow analysis was performed to test whether there were significant differences in observed versus expected composite events at 5 years. Because longer-term primary composite events and non-SCD death were competing risks, multivariable (adjusting for relevant variables

associated with outcomes in patients with HCM) survival analysis was performed by competing-risks regression analysis using the Fine-Gray proportional subhazards model, and subdistribution hazard ratios (sHRs) along with 95% confidence intervals (CIs) were calculated.^{22,23} In addition, competing-risks curves that demonstrate the events over time were created. Similarly, to assess for the association of various predictors with longer-term secondary composite outcomes, multivariable Cox proportional hazards analysis was used, and hazard ratios with 95% CIs were calculated. Only AFs noted during follow-up (>30 days in the operative group) were used in the survival analysis. Interactions between age and various predictors were tested. In addition, cross-collinearity was tested between multiple factors constituting the ESC risk score using the Spearman and Pearson correlation coefficients. Kaplan-Meier curves were generated to determine the cumulative proportion of patients with events as a function over time and were compared using the log-rank statistic. The discriminative abilities of survival models for longer-term composite events were compared using the c-statistic. Categorical net reclassification improvement was used to determine whether additional risk factors provided significant reclassification of risk for primary composite events (non-SCD deaths censored at the time of event). Statistical analyses were performed using SPSS version 11.5 (SPSS, Chicago, Ill), Stata version 10.0 (StataCorp, College Station, Tex), and R 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A *P* value <.05 was considered to indicate statistical significance.

RESULTS

The clinical and echocardiographic data of the study sample, as a whole and divided into 3 subgroups (low, intermediate, and high 5-year ESC SCD risk) are shown in [Tables 1](#) and [2](#). At a median of 51 days (IQR, 20-118 days) after the initial evaluation, 1160 patients (64%) underwent surgical relief of LVOT obstruction. Surgical details, along with differences in relevant characteristics of the entire study sample, separated by surgery and no surgery, are presented in the [Appendix E1](#) and [Table E1](#).

Outcomes

The mean total duration of follow-up for the study sample was 8.8 ± 4 years (median, 8.7 years; IQR, 6.3-11.3 years). During this time frame, a total of 185 deaths occurred, including 96 due to SCD, 58 with unknown etiology (but sudden death), 10 due to CHF, and 21 due to documented noncardiac causes. In addition, there were 39 (2%) appropriate ICD discharges. In patients who developed multiple endpoints (death or appropriate ICD discharge), the time to first event (ie, appropriate ICD discharge) was used as an event time cutoff. As a result, 169 patients (9%) met the primary composite endpoint (SCD, unknown but presumed SCD, and/or appropriate ICD discharge). The additional 31 patients who died due to CHF or documented noncardiac causes were not included in longer-term primary survival analysis (but constituted part of composite secondary events). There were no deaths in the 30 days (or before hospital discharge) following myectomy. In addition, 60 patients (3%) had sustained stroke, with no difference in rate between the surgical and nonsurgical

TABLE 1. Baseline characteristics of the study sample (n = 1809)

Variable	Total sample (n = 1809)	5-y ESC SCD risk			P value
		<4% (n = 1169)	4-6% (n = 326)	>6% (n = 314)	
Age, y, mean $\pm$ SD	50 $\pm$ 14	52 $\pm$ 12	46 $\pm$ 13	43 $\pm$ 12	<.001
Male sex, n (%)	1141 (63)	741 (63)	201 (62)	200 (64)	.12
Hypertension, n (%)	727 (40)	550 (47)	104 (32)	74 (24)	<.001
Diabetes mellitus, n (%)	180 (10)	139 (12)	25 (8)	16 (5)	.001
History of significant CAD, n (%)	266 (15)	201 (17)	35 (11)	30 (10)	<.001
Family history of HCM, n (%)	345 (19)	169 (15)	81 (25)	96 (31)	<.001
History of sudden death, n (%)	25 (1)	8 (0.7)	8 (2.5)	9 (2.9)	.002
Unexplained syncope, n (%)	315 (17)	41 (4)	96 (29)	178 (57)	<.001
History of atrial fibrillation	306 (17)	188 (16)	63 (19)	56 (18)	.35
History of stroke	64 (4)	49 (4)	8 (3)	7 (2)	.12
Implantable defibrillator	181 (10)	61 (5)	46 (14)	74 (24)	<.001
Permanent pacemaker	213 (11)	88 (8)	49 (15)	76 (24)	<.001
Beta-blockers, n (%)	1310 (73)	826 (71)	243 (75)	242 (77)	.05
Calcium channel blocker, n (%)	570 (32)	350 (30)	98 (30)	1225 (39)	.01
Disopyramide, n (%)	91 (5)	58 (5)	16 (5)	17 (5)	.35
Angina, n (%)	251 (14)	117 (10)	52 (16)	82 (26)	<.001
NYHA class, n (%)					
I	550 (30)	386 (33)	84 (26)	80 (26)	.04
II	908 (51)	554 (47)	181 (56)	173 (55)	
III/IV	351 (19)	229 (20)	61 (19)	61 (19)	
ACC/AHA major risk factors, n (%)					
None	1181 (65)	1003 (86)	143 (44)	153 (49)	<.001
1	476 (26)	144 (12)	154 (47)	153 (49)	
≥ 2	152 (8)	22 (2)	29 (9)	85 (27)	
5-y ESC SCD risk, %, mean $\pm$ SD	4.1 $\pm$ 0.8	2.5 $\pm$ 0.8	4.8 $\pm$ 0.6	9.0 $\pm$ 0.4	<.001

P values reflect comparison among 3 subgroups. ESC, European Society of Cardiology; SCD, sudden cardiac death; SD, standard deviation; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; ACC, American College of Cardiologists; AHA, American Heart Association.

subgroups (2.8% vs 3.1%; $P = .40$). No patient died due to stroke. Seventeen patients in the nonsurgical group progressed to NYHA class III or IV during follow-up but did not have LVOT obstruction >50 mm Hg to justify surgical myectomy. No patient required cardiac transplantation.

Association Between Observed and Predicted Events at 5 Years

We further studied the association between expected (based on ESC 5-year risk) and observed primary events at 5 years. In the entire study sample, 88 patients (4.9%) had a primary composite event at 5 years. Despite the wide range of expected event rates (2.5%-9%), the observed rate primary composite events at 5 years ranged from 4.6% to 5% across the 3 expected risk categories (Hosmer–Lemeshow P value = .32; Figure 1, A). Specifically, in the highest-risk category, despite an expected rate of 9%, the rate of observed events was only 4.8% at 5 years, potentially driven by a higher proportion of surgical myectomies. Of note, at 5 years, the rate of

primary events was 66% in patients classified as low risk by ESC risk score. Similarly, the rate of primary events at 5 years was 65% in patients with 0 ACC/AHA risk factors. The overall findings were similar in the subgroup that underwent surgical relief of LVOT obstruction (n = 1160; number of primary events at 5 years, 46). Even in this subgroup, despite a wide range of expected event rates (2.5%-8.6%), the rate of observed events at 5 years ranged from 3.6% to 4% across the 3 expected risk categories (Hosmer–Lemeshow test $P = .65$; Figure 1, B). Specifically, in the highest-risk category, despite an expected rate of 8.6%, the observed 5-year event rate was only 3.5%. In addition, at 5 years, the rate of primary events was 65% in patients who were classified as low risk by ESC risk score. Similarly, at 5 years, the rate of primary events was 63% in patients with 0 ACC/AHA risk factors.

Survival Analysis for Longer-Term Outcomes

Multivariable survival analysis for the primary composite outcome, using the competing risk assumptions are shown

TABLE 2. Echocardiographic parameters of the study sample

Variable	Total (n = 1809)	5-y ESC SCD risk			P value
		<4% (n = 1169)	4%-6% (n = 326)	>6% (n = 314)	
LV ejection fraction, %, mean $\pm$ SD	62 $\pm$ 5	62 $\pm$ 5	62 $\pm$ 5	62 $\pm$ 5	.45
Indexed LVED dimension, cm/m ² , mean $\pm$ SD	2.1 $\pm$ 0.3	2.1 $\pm$ 0	2.1 $\pm$ 0.3	2.1 $\pm$ 0.3	.52
Indexed LVED, cm/m ² , mean $\pm$ SD	1.2 $\pm$ 0.3	1.2 $\pm$ 0.4	1.2 $\pm$ 0.3	1.2 $\pm$ 0.2	.89
Maximal LV thickness, cm, mean $\pm$ SD	2.1 $\pm$ 0.5	2.0 $\pm$ 0.4	2.2 $\pm$ 0.5	2.4 $\pm$ 0.5	<.001
Indexed left atrial dimensions, cm/m ² , mean $\pm$ SD	2.2 $\pm$ 0.4	2.1 $\pm$ 0.4	2.3 $\pm$ 0.4	2.4 $\pm$ 0.4	<.001
Diastolic dysfunction, n (%)					.30
Abnormal relaxation	1664 (92)	1087 (93)	300 (92)	277 (88)	
Pseudonormal	127 (7)	82 (7)	18 (6)	27 (9)	
Restrictive physiology	18 (1)	0	8 (2)	10 (3)	
Resting mitral regurgitation, n (%)					.04
None	106 (6)	74 (6)	15 (5)	17 (5)	
Trivial to I+	1125 (62)	731 (63)	191 (59)	195 (62)	
$\geq$ II+	578 (32)	364 (31)	120 (37)	102 (32)	
Resting LVOT gradient (mm Hg), mean $\pm$ SD	46 $\pm$ 41	39 $\pm$ 39	51 $\pm$ 47	51 $\pm$ 42	<.001
Maximal LVOT gradient (mm Hg), mean $\pm$ SD	93 $\pm$ 40	88 $\pm$ 37	98 $\pm$ 45	105 $\pm$ 42	<.001
Exercise echocardiography, n (%)	1051 (58)	795 (68)	196 (60)	60 (19)	<.001
>100% age-sex predicted METs, n (%)*	610 (58)	509 (64)	81 (41)*	20 (33)*	<.001
Maximum METs achieved, mean $\pm$ SD	7.1 $\pm$ 1.2	7.6 $\pm$ 1.1	6.8 $\pm$ 1.1	6.4 $\pm$ 1.1	<.001
Abnormal BP response to exercise*	11 (1)	0	5 (3)*	6 (3)*	.01

ESC, European Society of Cardiology; SCD, sudden cardiac death; LV, left ventricular; SD, standard deviation; LVED, left ventricular end-systolic dimension; LVOT, left ventricular outflow tract; MET, metabolic equivalent; BP, blood pressure. *The percentages were derived only from those patients who underwent stress echocardiography.

in Table 3. In the present study sample, with a high proportion of patients with obstructive HCM undergoing surgery, neither ACC/AHA risk factors (0 vs $\geq$ 1; sHR, 1.19; 95% CI, 0.98-1.46; $P = .57$) nor ESC SCD risk score (sHR, 1.03; 95% CI, 0.95-1.12; $P = .46$) had any significant association with longer-term primary composite events, even on univariable competing-risks regression analysis. Findings were similar when ACC/AHA risk factors were entered into the analysis (Table 3). Competing-risks curves that demonstrate the events over time are shown in Figure 2. The incremental prognostic utility of various predictors for primary composite events,

in addition to ESC and ACC/AHA risk scores, is shown in Table 4.

The breakdown of longer-term primary composite events in patients, separated on basis of low, intermediate and high ESC SCD risk categories were not significantly different: 121 of 1169 (10%) for low, 28 of 326 (9%) for intermediate, and 22 of 314 (7%) for high SCD risk groups (log-rank statistic $P = .50$; Figure 3, A). Of note, 72% of primary composite events occurred in patients who were categorized as low-risk, based on ESC 5-year SCD risk criteria. Similarly, the breakdown of longer-term primary composite events in patients, separated on the basis of

FIGURE 1. Five-year expected versus observed composite events in the entire study sample (A) and the subgroup that underwent surgery during follow-up (B). SCD, Sudden cardiac death.

TABLE 3. Multivariable competing-risks regression analysis in the study population (n = 1809) based on the Fine–Gray proportional subhazards model (primary composite events, n = 169; additional non-SCD deaths, n = 31)

Variable	sHR (95% CI)	P value
Model A: with ESC SCD risk score		
Coronary artery disease	1.21 (1.03-1.99)	.03
NYHA class		
Class I: reference		
Class II	1.21 (1.04-1.36)	.01
Class III/IV	1.47 (1.10-1.19)	.002
AF during follow-up	1.51 (1.11-2.15)	<.001
ESC 5-y SCD risk	1.31 (0.75-2.25)	.36
Surgery to relieve LVOT	0.69 (0.47-0.83)	.001
Model B: with ACC/AHA SCD risk factors		
Coronary artery disease	1.23 (1.05-1.89)	.01
NYHA class		
Class I: reference		
Class II	1.20 (1.02-1.29)	.01
Class III/IV	1.50 (1.11-1.91)	.003
AF during follow-up	1.52 (1.09-2.035)	<.001
ACC/AHA risk factors (0 vs ≥ 1)	1.22 (0.95-1.51)	.62
Surgery to relieve LVOT obstruction	0.66 (0.42-0.78)	.001

In model A, the following variables were considered for the multivariable analysis: ESC 5-year SCD risk as a continuous variable, sex, NYHA class at initial visit, hypertension, cardiac medications at/after initial visit, AF during follow-up, surgery to relieve LVOT obstruction, and time to surgery. Variables that constituted part of ESC-endorsed SCD risk were not entered separately into the model. In model B, the following variables were considered for the multivariable analysis: ACC/AHA risk factors, age, sex, NYHA class at initial visit, hypertension, cardiac medications at/after initial visit, AF during follow-up, surgery to relieve LVOT obstruction, and time to surgery. Interactions between age and the following variables were nonsignificant: AF, LVOT, syncope, left ventricular wall thickness, and unsustained ventricular tachycardia. Because of nonsignificant cross-collinearity of the continuous variables that constitute part of the ESC risk score, further adjustment was not performed. sHR, Subdistribution hazard ratio; CI, confidence interval; ESC, European Society of Cardiology; SCD, sudden cardiac death; NYHA, New York Heart Association; AF, atrial fibrillation; LVOT, left ventricular outflow tract; ACC, American College of Cardiology; AHA, American Heart Association.

ACC/AHA risk factors, was not significantly different: 125 of 1222 (11%) for 0 risk factors, 34 of 451 (7%) for 1 risk factor, and 12 of 136 (8%) for ≥2 risk factors (log-rank $P = .40$; Figure 3, B). Almost three-quarters (74%) of primary composite events occurred in patients with 0 ACC/AHA risk factors. On the other hand, the breakdown of longer-term composite events in patients who underwent surgery versus those who did not undergo surgery was significant (87 of 1160 [8%] vs 82 of 649 [13%]; log-rank $P < .01$) (Figure 4).

The results of multivariable Cox proportional hazards analyses for the secondary composite outcomes are presented in Table E2.

DISCUSSION

In this study of adults with obstructive HCM with preserved LV ejection fraction managed at a high-volume surgical tertiary referral center (64% of whom underwent surgical relief of LVOT obstruction), we have demonstrated

FIGURE 2. Competing-risks curves demonstrating the events over time.

that despite a wide range of expected 5-year event rates based on ESC criteria (2.5%-9%), the observed events ranged from 4.6% to 5% across the 3 expected ESC SCD risk categories. Specifically, in the highest-risk category (>6% 5-year SCD risk), despite an expected rate of 9%, the rate was only 4.8% at 5 years. In addition, of all the primary composite events at 5 years, ~65% occurred in patients classified as low risk. Furthermore, ESC SCD risk score was not significantly associated with longer-term primary composite events (death and/or appropriate ICD discharge) on survival analysis. Moreover, ~70% of the longer-term composite events occurred in patients in the low ESC SCD risk score category, whereas only 7% of patients in the high-risk category had an event during longer-term follow-up. The findings were similar when ACC/AHA SCD risk factors were substituted for ESC risk score (Video 1).

Potential reasons for the underperformance of various SCD risk criteria in the present study include differences in specific patient populations studied, as well as regional differences in therapeutic management strategies. We only included patients who had obstructive (either at rest or with provocation) HCM physiology. We excluded patients with nonobstructed HCM, in whom the natural history and treatment considerations are very different from those with obstructed HCM.²⁴ The subgroup of nonobstructed patients includes a heterogeneous spectrum of patients including those in the early stages with mild HCM, truly nonobstructive late-stage burnt-out HCM, and apical HCM. Another major difference is that a high proportion of our patients underwent surgical relief of LVOT obstruction. Indeed, a significantly higher proportion of patients in the high SCD risk category underwent surgery and had a significantly lower-than-expected observed event rate.

TABLE 4. Synergistic and incremental prognostic utility of various models for longer-term primary composite events

Parameter	Model 1: Clinical model (ESC SCD risk score or ACC/AHA SCD risk factors)	Model 2: Clinical model + AF during follow-up	P value for difference between models 1 and 2	Model 3: Clinical model + AF during follow-up + myectomy	P value for difference between models 2 and 3
ESC-SCD risk score					
c-statistic	0.48 (0.31-0.64)	0.69 (0.60-0.77)	<.001	0.78 (0.70-0.84)	<.001
Categorical NRI		0.35 (0.15-0.51)	N/A	0.48 (0.24-0.67)	<.001
ACC/AHA SCD risk factors					
c-statistic	0.51 (0.29-0.62)	0.67 (0.59-0.77)	<.001	0.79 (0.710-0.87)	<.001
Categorical NRI	N/A	0.33 (0.13-0.48)	N/A	0.50 (0.21-0.65)	<.001

ESC, European Society of Cardiology; SCD, sudden cardiac death; ACC, American College of Cardiology; AHA, American Heart Association; AF, atrial fibrillation; NRI, net reclassification improvement; N/A, not applicable.

Thus, it appears that in patients with HCM, SCD risk stratification, especially based on current risk stratification (ESC or ACC/AHA criteria) could be further refined, based on regional differences in specific patient populations (obstructed vs nonobstructed), management strategies (including referral for surgery), and additional risk factors. It is important to understand that the ESC SCD risk criteria were developed using a combination of 7 categorical and continuous variables. Some of the continuous variables, such as left atrial size and LVOT gradient, have significant potential limitations due to a high degree of variability.² The left atrium is a 3-dimensional structure, and its dimensions can be measured erroneously very easily on 2-dimensional echocardiography. The use of 3-dimensional imaging potentially could reduce the variability and likely improve the classification of risk. Similarly, the LVOT gradient is dynamic and highly dependent on the patient's loading condition and medication status.

Indeed, there are conflicting data regarding the accuracy of the newer ESC risk predictor.^{4,5} In a North American analysis of 1629 patients with HCM, the authors argued

that most patients with sudden death or appropriate ICD discharges (60%) would have been misclassified as low risk based on ESC criteria and potentially would be unprotected if they did not receive an ICD. However, details of LVOT gradient or surgery were not reported in that study. This finding is similar to our observation that ~70% of composite events occurred in patients with a low ESC SCD risk score. In another European study of 706 patients with HCM from 2 tertiary care centers, the ESC criteria were shown to provide improved risk stratification compared with the standard ACC/AHA risk factors. However, the mean LVOT gradient (46 ± 44 mm Hg) and the proportion of patients undergoing surgical myectomy (20%) in that study were significantly lower compared with our present results, likely due to differences in referral patterns and individual patient management strategies. Thus, based on the results of the present study, it appears that the potential prognostic utility provided by the SCD risk stratification (based on either ESC or ACC/AHA criteria) is significantly modulated, especially in patients with obstructive HCM, by surgical relief of LVOT

FIGURE 3. Kaplan-Meier analysis demonstrating differences in longer-term composite events in the study sample, on the basis of 3 categories of 5-year risk for sudden cardiac death (SCD) based on ESC criteria (A) and on the presence of 0, 1, or ≥ 1 SCD risk factors based on ACC/AHA criteria (B). ESC, European Society of Cardiology; ACC, American College of Cardiology; AHA, American Heart Association.

FIGURE 4. Kaplan–Meier analysis demonstrating differences in longer-term composite events in the study sample, separated on the basis of surgery to relieve left ventricular outflow tract obstruction.

obstruction, and that this should be taken into account in future attempts at risk stratification.^{7,8}

As suggested previously, including in smaller reports of 125 and 244 patients,^{25,26} surgical relief of LVOT obstruction can result in improved outcomes, including reduced ICD discharge. There are many potential reasons for improvement in HCM-related outcomes following surgery. An obvious reason is LVOT obstruction and symptomatic relief, with resultant increased exercise capacity and improved longevity. Severe obstruction increases LV wall stress and reduces myocardial perfusion with resultant myocardial ischemia, which could potentially trigger malignant ventricular arrhythmias in already predisposed patients. In addition, long-standing pressure overload could lead to deleterious additional myocardial hypertrophy and fibrosis on top of the genetically present abnormal myocardium, which could then enhance the substrate for arrhythmias. An extensive surgical myectomy removes a substantial amount of hypertrophied muscle. Previous reports have demonstrated a significant association between LV hypertrophy and associated myocardial fibrosis.²⁷ Indeed, in a recent study, we demonstrated that surgical relief of LVOT obstruction is associated with long-term freedom from cardiac events (cardiac death and/or ICD therapy) compared with the absence of surgery.⁸ Moreover, additional markers, such as myocardial fibrosis (not evaluated in this study), also have potential roles in risk stratification, as noted previously.²⁸ A large-scale multicenter trial (HCMR; Novel Markers of Prognosis in Hypertrophic Cardiomyopathy) should help improve the risk stratification of patients with HCM.²⁹

Similarly, we also demonstrate that AF provides incremental prognostic utility in addition to standard risk stratification. Indeed, in a recent meta-analysis of 6858 patients with HCM, 1314 (19%) had a history of AF.³⁰ During follow-up, the mortality rate was 31% in patients

VIDEO 1. Dr Milind Y. Desai explains the importance and relevance of the paper. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30943-7/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30943-7/fulltext).

with AF and 18% in those without AF (odds ratio, 2.49; 95% CI, 1.85–3.35, $P < .00001$). Although increased AF-related mortality may be explained by stroke, systemic embolism, or side effects of warranted anticoagulation, some studies have shown an association between AF and increased risk of SCD.^{20,31} Some authors have theorized that AF might trigger ventricular arrhythmias,^{32,33} reduce the ventricular tissue refractory period,³³ be proarrhythmic through the short-long-short cycle length sequence,³⁴ and could affect cardiac output through loss of atrial kick.³⁵ In addition, AF could be a sign of increased catecholamines, which also would be an underlying stimulus for ventricular tachycardia.³⁶

Limitations

This retrospective observational study from a single tertiary center could have potential selection bias. Moreover, before the findings can be incorporated into clinical practice, these data need to be replicated in other centers, as well as prospectively. However, in HCM, most of the current data and practice guidelines/recommendations are based on observational retrospective studies and consensus opinions. The results of all testing were available to all clinicians at the time of decision making, introducing further bias. Previous SCD (ACC/AHA and ESC) risk stratification models were developed in a mixed HCM population and included unobstructed as well as apical variants. We wanted to validate these criteria in a group of patients with obstructed HCM because these constitute ~70% of all patients with

HCM. In addition, a large proportion of the cohort underwent surgical relief of LVOT obstruction, consistent with the referral pattern at our high-volume tertiary care center. However, this allowed us to test the hypothesis that surgery modulates difficult outcomes. Given the overall expertise involved with both the conservative and invasive management of HCM, our results might not be generalizable to other, less-experienced centers.^{37,38} Genetic testing and cardiac magnetic resonance data were not uniformly available and thus are not included in the analysis. In addition, some patients may present with silent AF that might have been missed on arrhythmia monitoring. Although we attempted to distinguish among various etiologies of cardiac death (eg, sudden vs CHF-related), it is very likely that some degree of misclassification occurred. As a result, we also report all-cause mortality, which is more objective and less biased than cardiac mortality. The basic results were similar.

CONCLUSIONS

In a large group of adults with obstructive HCM managed at a high-volume surgical tertiary referral center, we have demonstrated that despite a wide range of expected 5-year SCD event rates, the observed events were similar across the low, intermediate, and high SCD risk categories. In the highest SCD risk category, the expected rate was 9%, but the actual rate was only 4.8% at 5 years. The addition of AF and surgery to the SCD risk score significantly reclassified risk, along with providing incremental prognostic utility. Thus, factors such as AF, which potentially increases the risk of SCD, and surgical myectomy, which appears to mitigate the risk of SCD, might have to be considered during risk stratification (based on either ESC or ACC/AHA criteria).

Conflicts of Interest Statement

Dr Desai has previously consulted for Myokardia, Inc. All other authors have nothing to disclose with regard to commercial support.

References

- Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2011;124:e783-831.
- Elliott PM, Anastakis A, Borger MA, Borggreffe M, Cecchi F, Charron P, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733-79.
- O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010-20.
- Vriesendorp PA, Schinkel AF, Liebrechts M, Theuns DA, van Cleemput J, Ten Cate FJ, et al. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2015;8:829-35.
- Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European Society of Cardiology sudden death risk model for hypertrophic cardiomyopathy. *Am J Cardiol*. 2015;116:757-64.
- Maron MS, Olivetto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*. 2006;114:2232-9.
- Ommen SR, Maron BJ, Olivetto I, Maron MS, Cecchi F, Betocchi S, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:470-6.
- Desai MY, Smedira NG, Bhonsale A, Thamilarasan M, Lytle BW, Lever HM. Symptom assessment and exercise impairment in surgical decision making in hypertrophic obstructive cardiomyopathy: relationship to outcomes. *J Thorac Cardiovasc Surg*. 2015;150:928-35.e1.
- Kwon DH, Kapadia SR, Tuzcu EM, Halley CM, Gorodeski EZ, Curtin RJ, et al. Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation. *JACC Cardiovasc Interv*. 2008;1:432-8.
- Lever HM, Karam RF, Currie PJ, Healy BP. Hypertrophic cardiomyopathy in the elderly: distinctions from the young based on cardiac shape. *Circulation*. 1989;79:580-9.
- Kobayashi T, Dhillon A, Popovic Z, Bhonsale A, Smedira NG, Thamilarasan M, et al. Differences in global and regional left ventricular myocardial mechanics in various morphologic subtypes of patients with obstructive hypertrophic cardiomyopathy referred for ventricular septal myotomy/myectomy. *Am J Cardiol*. 2014;113:1879-85.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-63.
- Desai MY, Bhonsale A, Patel P, Naji P, Smedira NG, Thamilarasan M, et al. Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging*. 2014;7:26-36.
- Masri A, Pierson LM, Smedira NG, Agarwal S, Lytle BW, Naji P, et al. Predictors of long-term outcomes in patients with hypertrophic cardiomyopathy undergoing cardiopulmonary stress testing and echocardiography. *Am Heart J*. 2015;169:684-92.e1.
- Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165-93.
- Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, et al. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg*. 2008;85:127-33.
- Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circulation*. 2013;128:209-16.
- Kwon DH, Smedira NG, Thamilarasan M, Lytle BW, Lever H, Desai MY. Characteristics and surgical outcomes of symptomatic patients with hypertrophic cardiomyopathy with abnormal papillary muscle morphology undergoing papillary muscle reorientation. *J Thorac Cardiovasc Surg*. 2010;140:317-24.
- Maron BJ, Olivetto I, Spirito P, Casey SA, Bellone P, Gohman TE, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858-64.
- Ball W, Ivanov J, Rakowski H, Wigle ED, Linghorne M, Ralph-Edwards A, et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. *J Am Coll Cardiol*. 2011;58:2313-21.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.

23. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40:381-7.
24. Maron MS, Rowin EJ, Olivetto I, Casey SA, Arretini A, Tomberli B, et al. Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2016;67:1399-409.
25. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J*. 2007;28:2583-8.
26. An S, Fan C, Yang Y, Hang F, Wang Z, Zhang Y, et al. Long-term prognosis after myectomy in hypertrophic obstructive cardiomyopathy with severe left ventricular hypertrophy. *Cardiology*. 2018;139:83-9.
27. Kwon DH, Smedira NG, Rodriguez ER, Tan C, Setser R, Thamilarasan M, et al. Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. *J Am Coll Cardiol*. 2009;54:242-9.
28. Chan RH, Maron BJ, Olivetto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130:484-95.
29. Kramer CM, Appelbaum E, Desai MY, Desvigne-Nickens P, DiMarco JP, Friedrich MG, et al. Hypertrophic cardiomyopathy registry: the rationale and design of an international, observational study of hypertrophic cardiomyopathy. *Am Heart J*. 2015;170:223-30.
30. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM, et al. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. *Cardiovasc Diagn Ther*. 2017;7:36-44.
31. Tian T, Wang Y, Sun K, Wang J, Zou Y, Zhang W, et al. Clinical profile and prognostic significance of atrial fibrillation in hypertrophic cardiomyopathy. *Cardiology*. 2013;126:258-64.
32. Stafford WJ, Trohman RG, Bilsker M, Zaman L, Castellanos A, Myerburg RJ. Cardiac arrest in an adolescent with atrial fibrillation and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1986;7:701-4.
33. Boriani G, Rapezzi C, Biffi M, Branzi A, Spirito P. Atrial fibrillation precipitating sustained ventricular tachycardia in hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol*. 2002;13:954.
34. Denker S, Lehmann M, Mahmud R, Gilbert C, Akhtar M. Facilitation of ventricular tachycardia induction with abrupt changes in ventricular cycle length. *Am J Cardiol*. 1984;53:508-15.
35. Lerman BB. Mechanoelectrical feedback: maturation of a concept. *J Cardiovasc Electrophysiol*. 1996;7:17-9.
36. Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med*. 1976;294:1165-70.
37. Panaich SS, Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, et al. Results of ventricular septal myectomy and hypertrophic cardiomyopathy (from nationwide inpatient sample [1998-2010]). *Am J Cardiol*. 2014;114:1390-5.
38. Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Nishimura RA, et al. Low operative mortality achieved with surgical septal myectomy: role of dedicated hypertrophic cardiomyopathy centers in the management of dynamic subaortic obstruction. *J Am Coll Cardiol*. 2015;66:1307-8.

Key Words: hypertrophic cardiomyopathy, risk stratification

APPENDIX E1

Within the surgical group (n = 1160), the types of cardiac surgery were as follows: isolated myectomy, n = 766 (66%); myectomy plus mitral surgery, n = 255 (22%); myectomy plus coronary artery bypass grafting, n = 116 (10%); and myectomy plus coronary artery bypass plus additional surgery, n = 23 (2%). In the subgroup with concomitant mitral surgery, only 42 (15%) underwent valve replacement; the others underwent transaortic repair. During follow-up, 32 patients (3%) required a repeat surgical procedure to relieve LVOT obstruction (36, or 85%, requiring an additional mitral valve procedure). In addition, 135 patients (12%) underwent an invasive therapy (surgical MAZE or pulmonary vein isolation) for relief of

AF. In the surgical group, 947 patients (82%) patients underwent surgery following an initial evaluation (due to intractable symptoms or poor exercise tolerance), whereas 213 patients (18%) developed progressive CHF symptoms during longer-term follow-up that necessitated surgery. In the nonsurgical group, 60% patients were in NYHA class I at initial presentation and remained asymptomatic during follow-up. The remaining 649 patients were not offered surgery, because the symptoms (NYHA class II) were deemed to be adequately controlled with medical therapy, as recommended by the current guidelines.

The relevant characteristics of the study sample, presented on the basis of surgery versus no surgery, are shown in [Table E1](#).

TABLE E1. Relevant characteristics of the study sample, separated on basis of surgery versus no surgery (n = 1809)

Variable	No surgery (n = 649)	Surgery (n = 1160)	P value
Baseline			
Age, y, mean $\pm$ SD	50 $\pm$ 13	50 $\pm$ 14	.54
Male sex, n (%)	421 (65)	720 (62)	.12
History of significant CAD, n (%)	65 (10)	201 (17)	<.01
Family history of HCM, n (%)	135 (21)	210 (18)	.1
History of sudden death, n (%)	7 (1)	9 (1.6)	.2
Unexplained syncope, n (%)	81 (12)	234 (20)	.001
History of atrial fibrillation, n (%)	76 (12)	230 (20)	<.001
Implantable defibrillator, n (%)	60 (9)	121 (10)	.50
Beta-blockers, n (%)	446 (69)	864 (75)	.006
Calcium channel blocker, n (%)	175 (27)	395 (34)	<.05
Disopyramide, n (%)	20 (3)	71 (6)	<.001
Angina, n (%)	68 (10)	183 (16)	<.001
NYHA class, n (%)			
I	389 (60)	161 (14)	
II	260 (40)	648 (56)	
III/IV	0	351 (30)	<.001
ACC/AHA-endorsed major risk factors, n (%)			
None	416 (64)	765 (66)	
1	174 (27)	302 (26)	
≥ 2	59 (9)	93 (8)	.1
ESC 5-y SCD risk, n (%)			
<4%	455 (70)	714 (62)	
4%-6%	106 (16)	220 (19)	
>6%	88 (14)	226 (19)	.03
LV ejection fraction, %	61 $\pm$ 5	62 $\pm$ 5	.2
Maximal LV thickness, cm, mean $\pm$ SD	2.1 $\pm$ 0.5	2.1 $\pm$ 0.5	.6
Indexed left atrial dimensions, cm/m ² , mean $\pm$ SD	2.2 $\pm$ 0.4	2.3 $\pm$ 0.4	.1
Resting mitral regurgitation, n (%)			<.001
None	56 (9)	50 (4)	
Trivial to I+	430 (66)	694 (60)	
II+	163 (25)	246 (21)	
$\geq$ III+	0	170 (15)	
Maximal LVOT gradient, mm Hg, mean $\pm$ SD	74 $\pm$ 35	103 $\pm$ 39	<.001
Exercise echocardiography, n (%)	441 (68)	610 (53)	<.001
Maximum METs <7, n (%)*	0	610 (100)*	<.001
>100% age-sex predicted METs, n (%)*	0	610 (100)*	<.001
Maximum METs achieved, mean $\pm$ SD	8.2 $\pm$ 1.1	5.1 $\pm$ 1.1	<.001
Abnormal BP response to exercise, n (%)*	0	11 (2)*	<.001
Follow-up			
Atrial fibrillation, n (%)	101 (16)	260 (22)	.01
Nonsustained ventricular tachycardia, n (%)	61 (9)	120 (10)	.52
Sustained ventricular tachycardia, n (%)	6 (1)	12 (1)	.82
Permanent pacemakers, n (%)	55 (9)	136 (12)	.02
Implantable defibrillator, n (%)	133 (21)	233 (20)	.44

SD, Standard deviation; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; SCD, sudden cardiac death; LV, left ventricular; LVOT, left ventricular outflow tract; METs, metabolic equivalents; BP, blood pressure. *The percentages were derived only from those patients who underwent stress echocardiography.

TABLE E2. Multivariable Cox proportional hazards analysis for secondary composite outcomes (all-cause deaths and/or appropriate defibrillator discharge; n = 200)

Variable	HR (95% CI)	P value
Coronary artery disease	1.15 (1.01-2.11)	.04
NYHA class		
Class I: reference		
Class II	1.21 (1.03-1.39)	.01
Class III/IV	1.41 (1.10-1.97)	.01
ESC % 5-y SCD risk	1.22 (0.65-2.28)	.52
Surgery to relieve LVOT obstruction (time-dependent covariate)	0.77 (0.61-0.95)	.02
AF during follow-up	1.59 (1.15-2.10)	<.001

The following variables were considered for the multivariable model: ESC % 5-year SCD risk as a continuous variable, sex, NYHA class at initial visit, hypertension, cardiac medications at/after initial visit, AF during follow-up, surgery to relieve LVOT obstruction, and time to surgery. Interactions between age and following variables were nonsignificant: AF, LVOT obstruction, syncope, left ventricular wall thickness, and unsustained ventricular tachycardia. Because of nonsignificant cross-collinearity of the continuous variables that constitute part of the ESC risk score, further adjustment was not performed. Findings were similar when American College of Cardiology/American Heart Association risk factors were entered into the model. *HR*, Hazard ratio; *CI*, confidence interval; *NYHA*, New York Heart Association; *ESC*, European Society of Cardiology; *SCD*, sudden cardiac death; *LVOT*, left ventricular outflow tract; *AF*, atrial fibrillation. *Variables that constituted part of ESC-endorsed SCD risk were not entered separately in the model.