Prediction and Prevention of Sudden Death in Young Patients (<20 years) With Hypertrophic Cardiomyopathy

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Highly reliable identification of adults with hypertrophic cardiomyopathy (HC) at risk for sudden death (SD) has been reported. A significant controversy remains, however, regarding the most reliable risk stratification methodology for children and adolescents with HC. The present study assesses the accuracy of SD prediction and prevention with prophylactic implantable cardioverter-defibrillators (ICDs) in young HC patients. The study group is comprised of 146 HC patients <20 years of age evaluated consecutively over 17 years with prospective risk stratification and ICD decision-making. We relied on ≥1 established individual risk markers considered major within each patient's clinical profile, based on an enhanced American College of Cardiology /American Heart Association (ACC/AHA) guidelines algorithm. Of the 60 largely asymptomatic patients implanted with primary prevention ICDs at age 15 ± 4 years, 9 (15%) experienced device therapy terminating potentially lethal ventricular tachyarrhythmias and restoring sinus rhythm at 19 ± 6 years (range 9 to 29), 5.1 ± 6.0 years after implant; 3 patients had multiple appropriate ICD discharges. The individual risk marker algorithm was associated with 100% sensitivity in predicting SD events (95%CI: 69, 100) and 63% specificity for identifying patients without events (95%CI: 54, 71). Of these patients with device therapy, massive left ventricular hypertrophy (absolute wall thickness ≥30 mm) was the most common predictor, present in 70% of patients either alone or in combination with other risk markers. Each of the 146 study patients have survived to date at 22 ± 5 years, including all 86 without ICD recommendations. In conclusion, an enhanced ACC/AHA risk stratification strategy, based on established individual risk markers, was highly reliable in prospectively predicting SD events in children and adolescents with HC, and preventing arrhythmia-based catastrophes in this susceptible high risk population. **(Am J Cardiol 2020;128:75−83)**

The modern treatment era in hypertrophic cardiomyopathy (HC) has witnessed emergence of life-saving therapies such as implantable cardioverter-defibrillators (ICD) for sudden death (SD) prevention.[1−7] While this paradigm in HC management has been effective in adult patients,[2−4,7−9] controversy persists concerning the reliable strategy for SD prevention in young patients.[10−16] Also, concern has been raised that risk markers established and validated in adult HC populations may be less sensitive and specific in younger patients, potentially leading to either preventable SDs, or unnecessary implants in low risk patients.[10−22] Therefore, we believe it is timely to assess the accuracy of such previous considerations for young HC patients by interrogating the predictions and prevention of SD in our large cohort at Tufts Medical Center.

Methods

The database of the Hypertrophic Cardiomyopathy Institute at Tufts Medical Center, Boston, MA, was interrogated and 2,425 patients with a clinical diagnosis of HC were evaluated consecutively from 2001 to 2018. Of the 2,425 patients, 146 were <20 years of age at initial evaluation and comprise the present study population, representing a sub analysis of the overall Tufts HC cohort.

Survival status was systematically obtained to May 2019 by hospital visit or telephone contact with patients and/or family members and referring physicians (n = 142; 97%), or by Social Security death index in the absence of the most current follow-up (n = 4; 3%).

Clinical diagnosis of HC was based on echocardiographic or cardiac magnetic resonance (CMR) demonstration of a hypertrophied and nondilated left ventricle (LV) (maximum LV wall thickness ≥13 mm) in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy.[23,24] Patients identified with LV hypertrophy associated with systemic diseases or syndromes were excluded (e.g., RASopathies/Noonan syndrome; Fabry disease; or LAMP2 cardiomyopathy) as were patients with resuscitated cardiac arrests previous to evaluation in our center (n = 6).

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Sudden death was defined as unexpected sudden collapse occurring within 1 hour from the onset of symptoms in patients with a previously stable or uneventful clinical course. Potentially lethal cardiovascular events in which patients were successfully resuscitated from cardiac arrest (with documented ventricular fibrillation) or received appropriate ICD shocks are included in references to SD events.

Transthoracic echocardiographic studies were performed with a standard protocol. LV wall thickness was measured as the maximum dimension within the chamber (usually ventricular septum) at end-diastole. Peak instantaneous LV outflow gradient was estimated by continuous-wave Doppler and LV outflow obstruction was defined as a gradient ≥30 mm Hg at rest or with physiologic exercise.

CMR studies were obtained in 103 patients (71%) with 1.5 T scanners. Cine sequences were performed in standard views with full LV coverage. Late gadolinium enhancement (LGE) images were acquired 10 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid using a breath-held segmented inversion-recovery sequence. LGE quantification was performed as previously reported.[9]

Major clinical markers used to judge increased risk and guide ICD recommendations were based on consensus standards that included those risk factors prevailing during the time of this study, including an enhancement of the 2011 American College of Cardiology and American Heart Association (ACC/AHA) guidelines[23]: (1) family history of SD attributable to HC in ≥1 first or other close relatives; (2) unexplained recent syncope; (3) multiple repetitive and/or prolonged nonsustained ventricular tachycardia on ambulatory ECG monitoring; (4) diffuse and extensive LGE by contrast-enhanced CMR, either quantified (usually ≥15% of LV mass) or estimated by visual inspection, alone or with other markers; (5) end-stage phase, with systolic dysfunction (ejection fraction <50%); (6) LV apical aneurysm with regional scarring; (7) massive LV hypertrophy (wall thickness ≥30 mm). For each patient, risk assessment and ICD decisions were made prospectively in a standard fashion at initial visit or annual surveillance evaluation by senior cardiologists (EJR, BJM MSM).

One or more risk markers judged major within the overall clinical profile of a given patient, was sufficient evidence of increased SD risk to justify consideration and guide a prophylactic ICD recommendation.

Single- or dual-chamber ICDs with antitachycardia and antibradycardia pacing capabilities were implanted in 55 patients for primary prevention, and 5 other patient received subcutaneous devices. Patients underwent ICD placement at 15 ± 4 years (range 6 to 19), 41 based on 1 major risk marker, most commonly massive left ventricular hypertrophy (LVH; n = 19) or family history of HC-related SD (n = 14), and 19 others with 2 or more markers (Tables 1 and 2).

Stored intracardiac electrograms were analyzed by expert electrophysiologists for arrhythmias triggering defibrillator discharges (shocks or antitachycardia pacing), according to definitions reported in previous HC studies, that is, appropriate when triggered by ventricular fibrillation (VF) or rapid sustained ventricular tachycardua (VT; rate >200/min). Rate cutoffs for arrhythmia detection were programmed and antitachycardia pacing was activated at the discretion of the managing electrophysiologist.

Two age-specific models were combined to retrospectively calculate risk scores for patients in the overall study cohort at initial evaluation. In patients initially evaluated >16 years of age (n = 87) the mathematically derived quantitative European Society of Cardiology (ESC) risk score was calculated in accordance with O'Mahony et al to predict SD events over 5-years.[25,26] In patients <16 (n = 59) a similar "HCM Risk-Kids" score was applied, given that the ESC risk model excludes by design these pediatric patients.[16]

Patients were stratified into 3 risk subsets for ICD recommendations: low risk (<4% over 5 years; ICD not considered); intermediate risk (4% to 6% over 5 years) and high risk (≥6% over 5 years; ICD should be considered).[16,25,26] When an initial ICD intervention occurred >5 years after study entry, a second score was calculated at the clinical visit just previous to the time of delayed ICD therapy to account for possible changes in risk profile.

Data are expressed as mean ± standard deviation for continuous variables and proportions for categorical variables. Student's *t* test or Wilcoxon rank-sum tests addressed the statistical significance of continuous variables; chi-square or Fisher exact tests analyzed categorical variables. All tests were 2-sided and a p value <0.05 was considered statistically significant. For survival and event analyses, the fraction of patients at each follow-up interval was estimated by the Kaplan-Meier method.

For the purpose of sensitivity and specificity analyses, we defined true-positives as individuals who received recommendations for ICDs and subsequently experienced SD events; false-positives as patients who received recommendations for ICDs but did not subsequently experience an SD event; false negatives as patients who did not receive recommendations for ICDs but subsequently experienced SD events; and true negatives as patients who did not receive recommendations for ICDs or subsequently experience an SD event.

Using logistic regression, we analyzed the ability of these risk stratification approaches to discriminate between patients who experienced an SD event during follow-up and those who did not. Receiver operating characteristics curves were constructed by plotting sensitivity against 1 − specificity with the area under the curve expressed as the C statistic. The C statistic was calculated for the study cohort using either the enhanced ACC/AHA guidelines approach (i.e., the presence vs absence of the established major risk factors) or the ESC risk score.

This study was reviewed and approved by the Tufts Health Sciences Institutional Review Board, permitting use of patient medical information for research. All authors had full access and take responsibility for the integrity of the data, and agree to the article as written.

Results

Baseline characteristics of the 146 patients are detailed in Table 1. Mean age at the initial evaluation was 16 ± 3.2 years old (range 5 to 19): <10 years (n = 10); 10 to 15 years (n = 49); and 16 to 19 years (n = 87). Age at most

Table 1
Demographics and clinical parameters in 146 hypertrophic cardiomyopathy patients <20 years of age

Parameter	All HC patients <20 years at initial visit (n = 146)	Patients with primary prevention ICDs Yes (n = 60)	No (n = 86)	p value comparing patients with and without ICDs
Male	104 (71%)	39 (65%)	65 (76%)	0.23
Age at diagnosis (years)	14 ± 5	13 ± 6	15 ± 4	0.001
Age at first visit (years)	16 ± 3	16 ± 4	16 ± 3	0.82
Age at last evaluation (years)	22 ± 5	22 ± 5	21 ± 4	0.24
Family history of HC	76 (52%)	38 (63%)	38 (44%)	0.03
Family history − sudden death	32 (22%)	23 (38%)	9 (10%)	<0.001
Syncope	17 (11%)	14 (23%)	3 (3.5%)	0.001
NSVT on ambulatory monitoring	8 (5%)	6 (10%)	2 (2.3%)	0.11
Maximum LV wall thickness (mm)	20 ± 7	24 ± 7	17 ± 4	<0.001
Patients LV wall thickness ≥ 30mm	33 (23%)	33 (55%)	0	<0.001
LV apical aneurysm	0	0	0	-
Ejection fraction (%)	64 ± 6	65 ± 5	63 ± 6	0.009
Left atrial dimension (mm)	34 ± 6	35 ± 7	34 ± 6	0.38
Peak left ventricular outflow gradient, ≥ 30 mm Hg at rest	27 (18%)	18 (30%)	9 (10%)	0.006
Peak left ventricular outflow gradient, ≥ 30 mm Hg with exercise	48 (33%)	14 (23%)	34 (40%)	0.06
Left ventricular end-diastolic dimension (mm)	42 ± 6	40 ± 5	43 ± 6	0.001
Contrast-cardiac magnetic resonance				
Cardiac magnetic resonance studies	103	31	72	
Late gadolinium enhancement present	49 (47%)	21 (68%)	28 (39%)	0.01
Late gadolinium extent (%)	4.4 ± 3.7	6.2 ± 4.7	3.5 ± 2.4	<0.001
Late gadolinium extent LGE ≥ 15% of LV	2 (2%)	2 (6%)	0	0.66
NYHA-functional class, initial evaluation				
I	100 (69%)	36 (60%)	64 (74%)	0.005
II	31 (21%)	12 (20%)	19 (22%)	
III/IV	15 (10%)	12 (20%)	3 (3.5%)	
Atrial Fibrillation	4 (3%)	2 (3%)	2 (2%)	0.71
Septal myectomy	27 (18%)	19 (32%)	8 (9%)	0.001
Alcohol septal ablation	0	0	0	-
Heart transplant	3 (2%)	2 (3%)	1 (1%)	0.75
Primary prevention ICD, (%)	60 (41%)	60 (100%)	-	NA
Age at ICD implantation (years)	16 ± 4	15 ± 4	-	NA
Appropriate ICD Interventions	10 (7%)†	9	1†	
Resuscitated cardiac arrest	1 (0.7%)	0 (0%)	1†	NA
ICD complications	10 (17%)	10 (17%)	-	NA
Inappropriate shocks	8*	8*	-	
Device infection	0	0	-	
Lead fracture	4*	4*	-	
Drug therapy (number patients)				
Beta-blockers	75 (51%)	45 (75%)	30 (35%)	<0.001
Calcium antagonists	39 (27%)	20 (33%)	19 (22%)	0.19
Disopyramide	4 (3%)	4 (7%)	0	0.06
Genetic Testing	60	29	31	
MYBPC3	18	10	8	0.65
MYH7	9	6	3	0.40
TNNT2	4	2	2	0.95
MYL2, MYL3	3	2	1	0.95
TPM1	1	0	1	0.33
MYH7 + MYBPC3	1	1	0	0.97
NYHA-functional class, last evaluation‡				
I	110 (77%)	42 (70%)	67 (83%)	0.15
II	28 (20%)	15 (25%)	13 (16%)	
III/IV	4 (3%)	3 (5%)	1 (1%)	
Deaths	0	0	0	-

ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

Values as mean ± standard deviation, or number (% of subjects), when applicable.

* Includes 2 total patients with lead fracture and inappropriate shocks.

† Includes 9 patients with primary prevention ICD and 1 patient with secondary prevention ICD (a 17-year-old patient with a risk factor of family history of sudden death, who declined an ICD recommendation and subsequently experienced an out of hospital cardiac arrest. Two years after secondary prevention ICD placed patient had appropriate ICD shock terminating ventricular fibrillation).

‡ In 142 patients.

Table 2
Risk factors leading to primary prevention ICD implants and sudden death prevention among 60 hypertrophic cardiomyopathy patients <20 years of age

Risk markers	Risk factors leading to primary prevention ICDs (n = 60)	Risk factors leading to primary prevention ICDs in only patients with appropriate ICD therapy (n = 9)
Single	41	6
Massive LVH	19	4
Family history of SD	14	1
Unexplained syncope	5	1
NSVT	3	0
Left ventricular apical aneurysm	0	0
End-stage HC	0	0
Extensive LGE	0	0
Two	18	3
Massive LVH + Family history of SD	5	0
Massive LVH + Syncope	4	0
Massive LVH + NSVT	3	2
Family history SD + Syncope	2	0
Family history SD + End-stage	1	0
Massive LVH + Extensive LGE	1	1
Syncope + NSVT	1	0
End-stage + Extensive LGE	1	0
Three or more	1	0
Massive LVH + Syncope + Family of SD	1	0

LGE = late gadolinium enhancement on cardiac magnetic resonance; ≥15% of left ventricular mass; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; multiple/repetitive/prolonged episodes on ambulatory monitoring; SD = sudden death.

recent evaluation was 22 ± 5 years; 104 patients (71%) were male. Maximum LV wall thickness was 20 ± 7 mm, including 32 patients (22%) ≥30 mm. Ventricular septal Z-score was 11 ± 6, including 106 patients (73%) with Z-score > 6.

At initial evaluation, most patients (131; 90%) were asymptomatic or only mildly symptomatic (NYHA functional classes I/II); and at most recent evaluation the vast majority (138; 98%) remained in classes I/II. Duration from initial evaluation and study entry at Tufts Medical Center to most recent follow-up was 5.8 ± 4 years (range to 16 years).

Of the 60 patients with primary prevention ICDs, 9 (15%) experienced 1 or more appropriate ICD shocks for VF (n = 6) or rapid monomorphic VT (n = 3) to restore sinus rhythm (Figures 1 and 2). Device therapy occurred at 19 ± 6 years of age, including 5 at <20 years and 4 at ≥20 years (range 9 to 29) (Table 3), and occurred 5.1 ± 6.0 years (range 0.1 to 16) after implant, including 7 patients with transvenous ICDs and 2 with subcutaneous ICDs. One year and 5 year cumulative probability for first appropriate ICD intervention was 3.4% (95%CI: 0.01, 12.8%) and 14.0% (95%CI: 6.9, 27.5), respectively. Four patients had multiple therapies (2 to 5) including one who also experienced a VT storm.

Of the 9 patients with appropriate ICD therapy, 6 (67%) had 1 major risk marker: that is, massive LV hypertrophy (n = 4), family history of SD (n = 1), and unexplained recent syncope (n = 1; Table 2 and 3). Only 3 patients (33%) had 2 risk markers: massive LV hypertrophy and multiple episodes of nonsustained VT (n = 2) or massive hypertrophy and extensive LGE (n = 1). Therefore, massive LV hypertrophy was the most common risk marker (n = 7), alone in 4 patients and associated with other markers in 3.

Of the 60 patients with primary prevention ICDs, 10 (17%) experienced device related complications, 5.1 ± 2.5 years from implant, predominantly inappropriate shocks triggered by sinus and supraventricular tachycardia in 6 patients, and lead fractures in 4 (2 resulting in inappropriate shocks); 2 of these 10 patients also had appropriate device therapy.

Over follow-up, there were no deaths related to HC or other causes among the 146 study patients, including 38 patients who survived to ≥25 years (and 6 patients to ≥30 years). Three nonobstructive patients underwent heart transplant for progressive refractory heart failure (1 with systolic dysfunction and 2 with preserved EF, at ages 17 to 34 years); 25 other patients had surgical septal myectomy for drug-refractory heart failure symptoms due to LV outflow obstruction at age 17 ± 4 years (range 7 to 26 years), with sustained improvement in symptoms to NYHA class I/II in 24 (96%), 4.3 ± 3.6 years postoperatively.

Utilizing the ACC-AHA Guideline risk markers, the C-statistic for the study cohort was 0.81 (95%CI: 0.77, 0.85) (Table 4). Sensitivity for predicting SD events was 90% (95%CI: 51, 99); or 100% as an intention to treat (95%CI: 69, 100). Specificity for predicting patients without events was 63% (95%CI: 54, 71). Number of patients required to treat with ICDs to save 1 patient with terminated VT/VF was 6.9.

In contrast, applying the European risk models to our cohort, the C-statistic using the 2 European risk models was 0.68 (95%CI: 0.52, 0.85; Table 4). Sensitivity for predicting SD events using high risk scores ≥6%/5 years was 60% (95%CI: 26, 87); specificity for predicting patients who did not experience SD events was 76% (95%CI: 68, 83). Number of patients required to treat with ICDs to save 1 patient with terminated VT/VF was 7.7.

Discussion

Sudden unexplained death has been a highly visible consequence of HC, even leading to characterization of this disease as the most common cause of arrhythmia-related events in the young.[27,28] Paradoxically, in clinical practice HC is uncommonly identified in children and adolescents, and there has also been concern for the not inconsequential complication risk associated with prophylactically implanted ICDs over long periods of time in young patients.[10–22,29] Nevertheless, our positive experience in reducing SD events in largely adult HC patients with ICDs[2,8] dictated the aggressive device-related strategies reported here in younger patients.

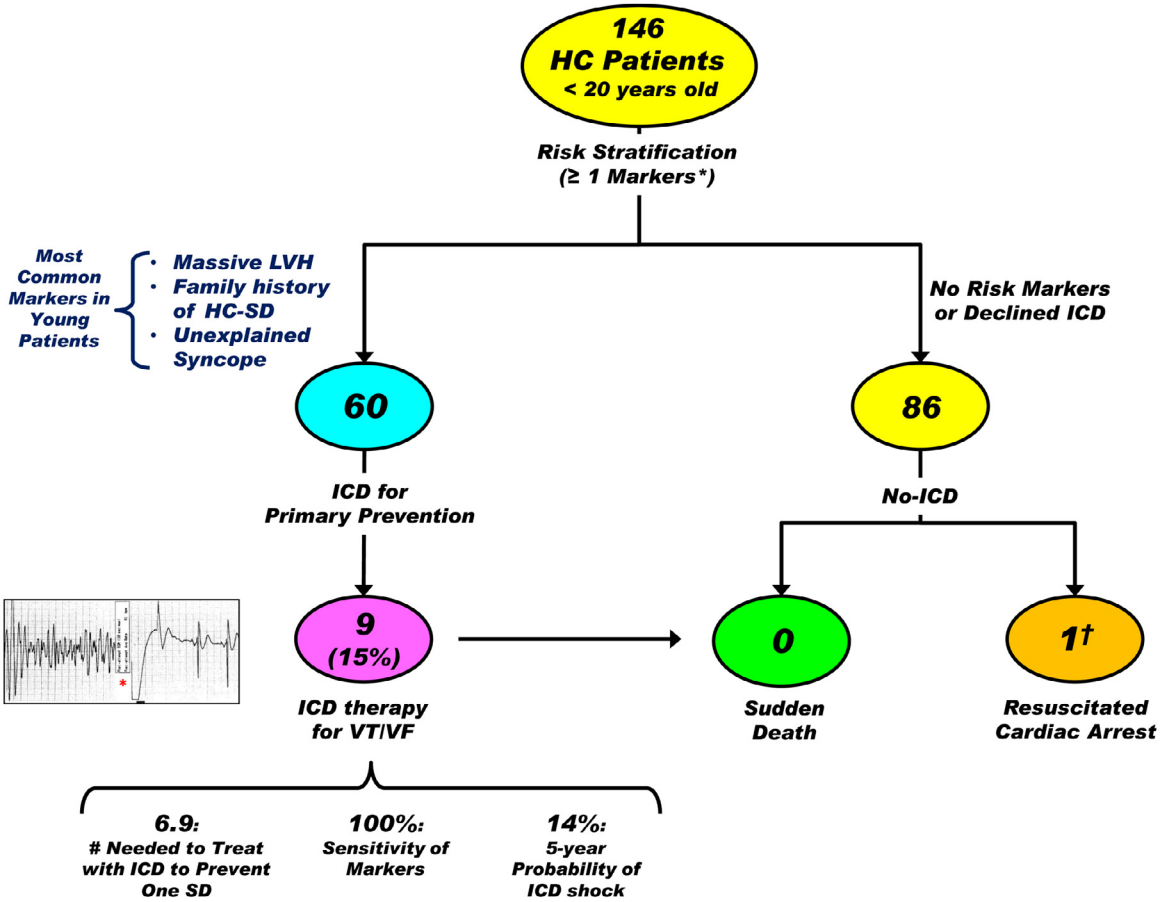

Figure 1. Events among 146 children and adolescents with HC. Among 146 patients, 60 underwent primary prevention implantable cardioverter defibrillators placement, terminating 9 sudden death events. No sudden death occurred among the 86 patients without ICDs. The patient with out-of-hospital resuscitated cardiac arrest (†) had a family history of HC-related SD and had previously declined a primary prevention ICD.*: Risk markers include: (1) family history of SD attributable to HC in ≥1 first or other close relatives; (2) unexplained recent syncope; (3) multiple repetitive and/or prolonged nonsustained ventricular tachycardia on ambulatory ECG monitoring; (4) diffuse and extensive LGE by contrast-enhanced CMR, either quantified (usually ≥ 15% of LV mass) or estimated by visual inspection, alone or with other markers; (5) end-stage phase, with systolic dysfunction (ejection fraction < 50%); (6) LV apical aneurysm with regional scarring; (7) massive LV hypertrophy (wall thickness ≥30 mm). HC = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; SD = sudden death.

With prospective decision-making, employing ≥1 established major risk markers to our study cohort, over follow-up we were able to document a significant number of ICD-aborted SDs and the absence of HC-related mortality. Indeed, 15% of patients implanted for primary prevention experienced life-saving device therapy terminating potentially lethal ventricular tachyarrhythmias, with rate of appropriate ICD interventions 3.4% at 1-year and 14% at 5-years, similar to that reported in other adult and pediatric HC cohorts.[1–3,7–9,11–19] Notably, timing of first appropriate ICD therapy varied widely in our cohort from a few months to as long as 16 years after implant, underscoring the unpredictability of the underlying myocardial substrate in HC and the difficulty in precisely predicting the timing of events in individual patients. Inappropriate shocks occurred in about 15% of patients, similar to the current experience in adults HC patients,[3,30,31] and only 4 patients have experienced major ICD complications (e.g., lead fractures); 2 of these also had appropriate device therapy.

It has been suggested that risk factors used to select adult HC patients for ICDs may not be entirely applicable to younger patient populations in pediatric cardiology practice, raising the concern that some patients could be left vulnerable to SD due to limitations of the risk stratification algorithm in this younger age group.[13–16] However, in contrast, we found that the enhanced ACC/AHA risk marker strategy conveyed excellent sensitivity by prospectively identifying children and adolescent patients with subsequent SD events (i.e., sensitivity approaching 100%), and no patient in this study cohort judged with insufficient risk to justify a prophylactic ICD had an event. Notably, the C-statistic of 0.81 in our prospective application of these enhanced ACC/AHA risk markers in these young patients is superior to that of European risk scores applied to either adult or pediatric HC patient cohorts.[16,25,26]

Massive LV hypertrophy was the predominant risk predictor present in 75% of those young patients who experienced appropriate ICD therapy, either alone or in combination with other markers. Relying on our previous data and the enhanced ACC/AHA guidelines, we elected to define massive LV hypertrophy here by an absolute LV wall thickness of ≥30 mm independent of age and body

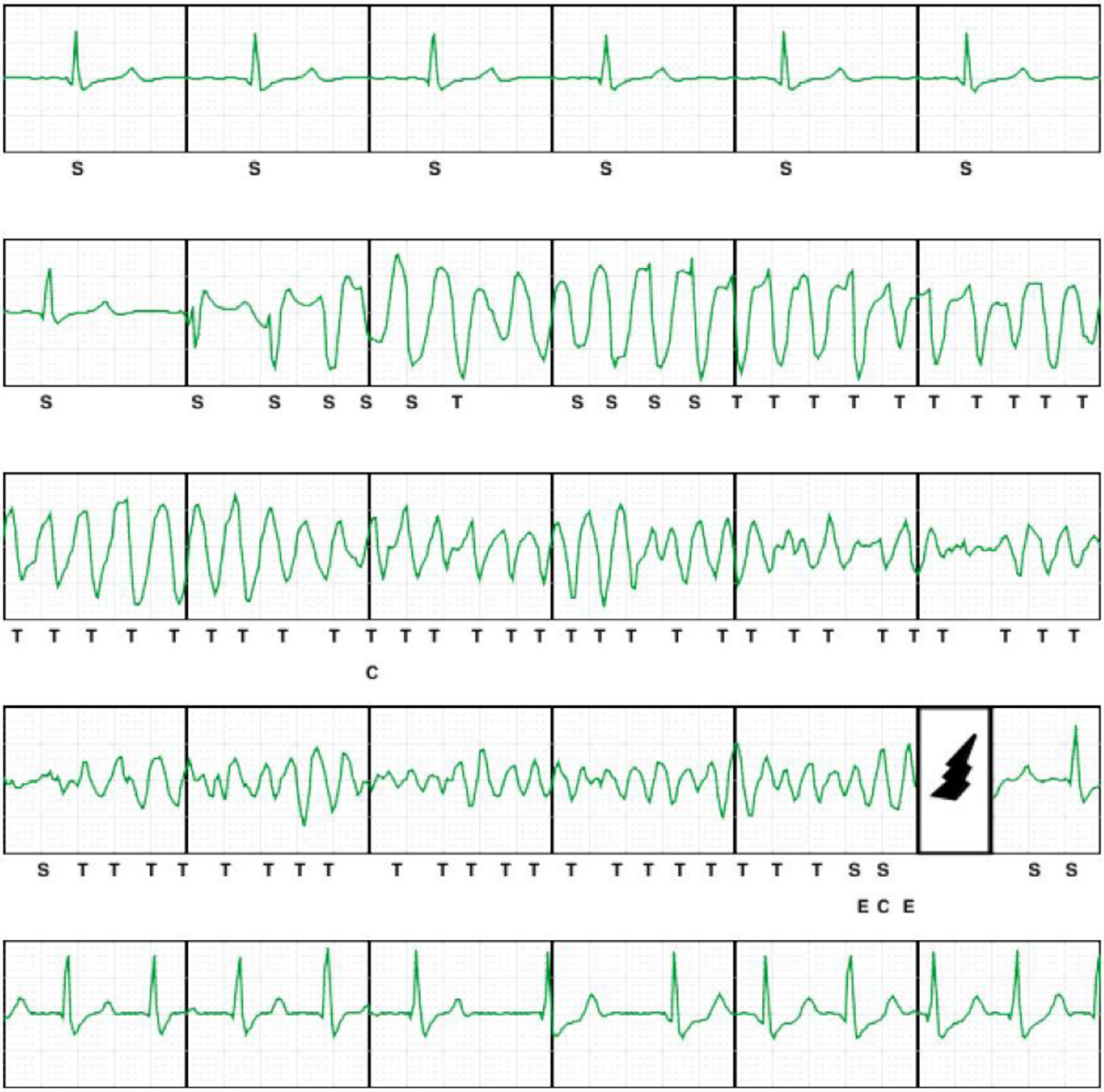

Figure 2. Stored electrogram showing an ICD shock terminating polymorphic VT and restoring sinus rhythm in a 21-year-old man 2 years after receiving a primary prevention (subcutaneous) ICD in the setting of massive left ventricular hypertrophy, wall thickness of 30 mm.

size.[9,23,32,33] However, other investigators have proposed utilizing LV wall thickness indexed to body surface area in children to account for morphologic changes concomitant with growth and maturation.[10,14,24] In this regard, a Z-score of ≥6 has been proposed as the equivalent of massive LV hypertrophy and a major risk marker for HC-related SD in children.[10,14,24] However, we found that about 75% of our cohort had Z-scores ≥6, excluding this measure of LV wall thickness as a reliable predictor of future events that would undoubtedly lead to excessive ICD implants in otherwise low-risk patients.

Furthermore, the most common markers associated with ICD therapy providing protection against SD in young patients, are also reliable markers in adults, that is, recent unexplained syncope, family history of SD in a close relative, and massive LV hypertrophy.[2,9,23,30,34] Conversely, some risk factors useful in adults do not have the same relevance to younger patients since they probably develop over substantial periods of time, including end-stage disease, LV apical aneurysm, and extensive LGE which together represent a sizeable subset of high risk adult patients with ICD interventions.[2,4,35]

In contrast to the individual risk marker strategy based on an enhanced ACC/AHA recommendations used here, other investigators have previously proposed alternative approaches.[16,24−26] For example, a novel but controversial strategy has been proposed for patients <16 years old with LVH including some with sarcomeric HC, utilizing the

Table 3
HC Patients with appropriate ICD interventions or resuscitated cardiac arrests

Primary prevention ICD intervention																	
Patient	Sex	Age at ICD implant, (years)	Time from ICD implant to event, (years)	Age at ICD event, (years)	NYHA initial	NYHA final	Myectomy	EF, (%)	LVOTG rest, (mm Hg)	LA, (mm)	Max LV thickness, (mm)	Massive LVH[§]	FH of SD	Syncope	Number ACC/ AHA risk markers	Risk score, (%/5y)	Number ICD events
1	M	9	0.1	9	1	1	0	70	0	30	26	0	0	+	1	19	2[¶]
2	M	11	4	15	2	3	0	65	40	31	33	+	0	0	2[†]	6.9	1
3	M	13	17	30	1	1	0	65	0	41	28	+	0	0	2[‡]	8.2	1
4	F	13	14	27	3	2	+ *	75	100	31	33	+	0	0	1	4.4	2[#]
5	M	15	0.6	16	1	1	0	75	15	43	36	+	0	0	1	11.5	1
6	F	16	1	17	1	1	0	60	0	38	23	0	+	0	1	7.9	1
7	M	16	3	19	2	1	0	55	0	35	30	+	0	0	1	3.1	2**
8	M	17	5	23	3	2	+ *	65	50	44	40	+	0	0	2[‡]	7.0	5[††]
9	M	19	2	21	1	1	0	65	30	32	30	+	0	0	1	3.1	1
Resuscitated Cardiac Arrest																	
Patient	Sex	Age at ICD implant, (years)	Time from ICD implant to event, (years)	Age at ICD event, (years)	NYHA initial	NYHA final	Myectomy	EF, (%)	LVOTG rest, (mm Hg)	LA, (mm)	Max LV thickness, (mm)	Massive LVH	FH of SD	Syncope	Number ACC/ AHA risk markers	Risk Score, (%/5 y)	Number ICD events
10	F	17	6	23	1	1	0	60	0	35	15	0	+	0	1	3.3	1[‡‡]

EF = ejection fraction; F = female; FH= family history; ICD = implantable cardioverter-defibrillator; LA = left atrium; LV = left ventricular; LVH = left ventricular hypertrophy; LVOTG = left ventricular outflow tract gradient; M = male; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SD = sudden death.

* myectomy previous to initial ICD shock.

† extensive LGE on CMR represents one risk marker.

‡ NSVT on ambulatory monitoring represents one risk marker.

§ left ventricular wall thickness ≥30 mm.

¶ Subsequent ICD intervention 4 years after initial device discharge.

Subsequent ICD intervention 1 years after initial device discharge.

** Subsequent ICD intervention 6 months after initial device discharge.

†† Subsequent ICD intervention 6, 10, 11 years after initial device discharge. Transplant at age 33.

‡‡ Subsequent appropriate ICD intervention at age 25.

Table 4
Sensitivity and specificity for sudden death prevention based on 2019 enhanced ACC/AHA guidelines and risk scores in HC patients ≥16 years (n = 87) and <16 years (n = 59)

Risk category	Enhanced ACC/AHA guidelines	Combined European risk score	ESC risk score ≥ 16 years †	Risk score (HC risk-kids) <16 years †
Sensitivity (to prevent SD)	100%* (69,100) (90% [51,99])	60% (26,87)	40% (5,85)	80%(28,99)
Specificity (likelihood detecting patients not at SD risk)	63% (54,71)	76% (68, 83)	90% (81,92)	56% (42,70)
Positive Predictive Value	16% (14,20)	16% (9, 25)	20% (7,47)	14% (9,22)
Negative Predictive Value	100% (93,100)	96% (92, 98)	96% (92,98)	97% (84, 99)
C-statistic	0.81 (0.77, 0.85)	0.68 (0.52,0.85)	0.65 (0.41, 0.89)	0.68 (0.48, 0.89)

* Includes intention to treat, a 17-year-old patient with a risk factor of family history of sudden death, who declined an ICD recommendation and subsequently experienced an out of hospital cardiac arrest.
† assumes ICD implanted in patients with only high risk scores (≥6%/5 years).

quantitative ESC risk score, "HCM-Risk-Kids."[16] These risk scores when applied to our cohort, had higher specificity for choosing patients unlikely to have events, possibly decreasing the number of implants in low-risk patients. However, sensitivity for identifying individual patients at risk for SD events was only 60%, i.e., over one-third of our patients implanted based on individual ACC/AHA markers who experienced appropriate device therapy would not have received an ICD recommendation, leaving them vulnerable to SD.

Alternatively, ESC guidelines have advocated using 2 or more major risk markers as the threshold for a primary prevention ICD recommendation in young HCM patients.[24] However, that strategy (if used here) would have been highly insensitive for preventing SD events, since two-thirds of our patients who experienced appropriate device therapy were implanted for only 1 risk marker and therefore would not have been protected from SD if 2 markers had been required for a prophylactic and preventive implant. The present referral population was an advantage providing the opportunity to identify and treat high risk patients and thereby demonstrate the power of the ICD for prevention of SD.

In conclusion, with prospective decision-making employing established individual risk markers in a consecutive referral-based HC cohort of children and adolescents, we were able to reliably identify at-risk patients, and prevent SD events with selective use of prophylactic ICDs. Massive hypertrophy (LV wall thickness of ≥ 30 mm) proved to be the predominant risk factor for predicting SD events terminated by ICDs, either alone or in combination with other markers.

Authors' Contributions

Ethan J. Rowin: Conceptualization, Methodology, Data Curation, Writing- Original Draft, Visualization; Aadhavi Sridharan: Methodology, Data Curation, Formal analysis, Writing- Review & Editing; Christopher Madias: Writing- Review & Editing, Supervision; Chris Firely: Data Curation, Formal analysis, Writing- Review & Editing; Benjamin Koethe: Data Curation, Formal analysis, Writing- Review & Editing; Mark S. Link: Writing- Review & Editing, Supervision; Martin S. Maron: Conceptualization, Methodology, Writing- Review & Editing, Supervision; Barry J. Maron: Conceptualization, Methodology, Writing- Review & Editing, Supervision.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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