Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 61, No. 14, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.037

Prevention of Sudden Cardiac Death With Implantable Cardioverter-Defibrillators in Children and Adolescents With Hypertrophic Cardiomyopathy

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Objectives The aim of this study was to determine the efficacy of implantable cardioverter-defibrillators (ICDs) in children and adolescents with hypertrophic cardiomyopathy (HCM).

Background HCM is the most common cause of sudden death in the young. The availability of ICDs over the past decade for HCM has demonstrated the potential for sudden death prevention, predominantly in adult patients.

Methods A multicenter international registry of ICDs implanted (1987 to 2011) in 224 unrelated children and adolescents with HCM judged at high risk for sudden death was assembled. Patients received ICDs for primary (n = 188) or secondary (n = 36) prevention after undergoing evaluation at 22 referral and nonreferral institutions in the United States, Canada, Europe, and Australia.

Results Defibrillators were activated appropriately to terminate ventricular tachycardia or ventricular fibrillation in 43 of 224 patients (19%) over a mean of 4.3 ± 3.3 years. ICD intervention rates were 4.5% per year overall, 14.0% per year for secondary prevention after cardiac arrest, and 3.1% per year for primary prevention on the basis of risk factors (5-year cumulative probability 17%). The mean time from implantation to first appropriate discharge was 2.9 ± 2.7 years (range to 8.6 years). The primary prevention discharge rate terminating ventricular tachycardia or ventricular fibrillation was the same in patients who underwent implantation for 1, 2, or ≥3 risk factors (12 of 88 [14%], 10 of 71 [14%], and 4 of 29 [14%], respectively, p = 1.00). Extreme left ventricular hypertrophy was the most common risk factor present (alone or in combination with other markers) in patients experiencing primary prevention interventions (17 of 26 [65%]). ICD-related complications, particularly inappropriate shocks and lead malfunction, occurred in 91 patients (41%) at 17 ± 5 years of age.

Conclusions In a high-risk pediatric HCM cohort, ICD interventions terminating life-threatening ventricular tachyarrhythmias were frequent. Extreme left ventricular hypertrophy was most frequently associated with appropriate interventions. The rate of device complications adds a measure of complexity to ICD decisions in this age group.
(J Am Coll Cardiol 2013;61:1527–35) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LV = left ventricular
LVH = left ventricular hypertrophy
SD = sudden death
VF = ventricular fibrillation
VT = ventricular tachycardia

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death (SD) in young people, including competitive athletes (1). Indeed, SD has been the most visible and devastating, as well as unpredictable, complication of this disease since its contemporary description >50 years ago (1,2). During the past decade, implantable cardioverter-defibrillators (ICD) have proved effective in preventing SD in patients with HCM, but largely in adults (3,4). Because there are few data focusing on pediatric patients with HCM (5–8), uncertainty persists as to the effectiveness and reliability of ICDs in this age group and

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the selection of patients who would most likely benefit from this therapy (1,9,10). This consideration is most relevant to translating the risk factor model currently used in the selection of adult patients with HCM for ICDs to much younger patients (1). Therefore, we assembled a large and novel cohort of children and adolescents with HCM and ICDs, judged at high risk for SD, to assess criteria for implantation and subsequent clinical outcomes.

Methods

Patient selection. The study group comprised 224 patients with HCM, <20 years of age, who received ICDs at 22 participating institutions in the United States, Canada, Europe, and Australia. All patients with HCM who underwent implantation for high-risk status at participating institutions from 1987 to 2011 constituted the study group. Decisions regarding ICD implantation were made at the discretion of managing pediatric cardiologists and electrophysiologists, relying largely on the risk stratification model established for the prevention of SD in patients with HCM (1,9,10).

Of 224 study patients, selected data from 24 had been included in an earlier investigation (4) but are reported herein with extended follow-up. Approval was received from institutional review boards, or the equivalent, for all participating institutions, with consent obtained from all participants.

Defibrillators. Initially, single-chamber or dual-chamber ICDs were implanted with transvenous (n = 185) or epicardial (n = 39) lead systems with capacity for antitachycardia and antibradycardia pacing. During follow-up, all patients received updated ICDs with memory for recording and storing electrocardiographic data. Devices were implanted according to customary practice, with defibrillation thresholds tested to verify successful termination of ventricular tachyarrhythmias. Antitachycardia pacing was activated at the discretion of managing electrophysiologists.

Definitions. HCM. Each patient had a clinical diagnosis of nonsyndromic HCM on the basis of 2-dimensional echocardiographic or cardiovascular magnetic resonance evidence of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease that could account for the magnitude of hypertrophy evident (9–11). Patients with left ventricular (LV) hypertrophy (LVH) as a component of systemic disease or syndromes (e.g., Noonan syndrome, *LAMP2* cardiomyopathy [Danon disease]) (12) were excluded (11).

Maximum LV wall thickness was ≥15 mm (mean 28 ± 8 mm; range: 15 to 53 mm) in 188 patients, consistent with HCM diagnosis at any age (9,10,13). LV thickness was <15 mm in 36 other patients (mean 12 ± 2 mm; *z*-score range: 2.2 to 12; mean 5 ± 2) (14). In 74 patients, extreme LVH was defined as an absolute maximal thickness ≥30 mm (mean 35 ± 5 mm; range: 30 to 51 mm) (15), in accord with prior studies (4,9,15). In the 43 patients with LV thickness <30 mm (to 29 mm; mean 24 ± 5 mm), the mean *z*-scores was 18 ± 5 (range to 30).

Of the 224 patients, 172 (77%) had evidence most consistent with sarcomeric HCM, including ≥1 of the following: 1) family history of HCM (n = 122, including 78 with HCM-related SD); prior surgical myectomy (n = 43) or alcohol ablation (n = 1) to relieve outflow obstruction; rest gradient ≥ 30 mm Hg at the time of implantation (n = 54); sarcomere protein mutation (n = 49) (16): *MYH7* (n = 23), *MYBPC3* (n = 8), *TNNT2* (n = 5); *MYL2* (n = 2); *TPM1* (n = 2); *TNN13* (n = 2); compound *MYBPC3* (n = 3); double: *MYH7* and *MYBPC3*; *MYBPC3* and *TNNI3*; *MYH7* and *CAV3*; *MYBC3* and *ACTC1* (n = 1 each).

EVENTS. On the basis of stored electrographic analysis by expert electrophysiologists at each center, defibrillator discharges were regarded as appropriate when triggered by ventricular fibrillation (VF) or rapid ventricular tachycardia (VT) (heart rate >150 beats/min) (1,9,10). Interventions were considered inappropriate when triggered by heart rates exceeding the programmed threshold, as a consequence of

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Manuscript received October 10, 2012; revised manuscript received December 29, 2012, accepted January 2, 2013.

sinus tachycardia, supraventricular arrhythmias, or device or lead malfunction.

FOLLOW-UP. The duration of follow-up was computed from initial ICD implantation to first appropriate device intervention or death, whichever occurred first. In patients without appropriate ICD discharges, follow-up duration (≥6 months) was terminated at the most recent evaluation (clinic visit or telephone contact) as of March 2012 or at heart transplantation or death.

Risk factor analysis. In judging SD risk level, managing cardiologists considered the following (1,3,4,9,10,13,15,17–19): for secondary prevention, prior cardiac arrest (with documented VF or sustained VT); and for primary prevention, 1) family history of premature HCM-related SD (n = 78), 2) extreme LVH (n = 117), 3) unexplained syncope inconsistent with neurocardiogenic origin (n = 71), 4) nonsustained VT on 24-h ambulatory (Holter) electrocardiogram (≥3 beats ≥120/min) (n = 22), and 5) hypotensive blood pressure response to exercise (n = 33).

Statistical analyses. Rates of appropriate ICD discharges were calculated according to time between implantation and first appropriate intervention. Confidence intervals (CIs) were derived using the bootstrap method. Specifically, 1,000 bootstrap samples were drawn with replacement, using simple random sampling (95% CI: 2.5th to 97.5th percentiles of samples). Rates were compared among patient subgroups using chi-square tests for heterogeneity and trend or Student's *t* tests, as appropriate. Chi-square goodness-of-fit tests were used to assess uniformity. Cox proportional hazards analysis was used to compare ICD intervention rates. The probability of appropriate ICD intervention was estimated using the Kaplan-Meier method with subgroups compared using log-rank tests.

For continuous variables, data are expressed as mean ± SD. The p values are 2-sided and considered statistically significant at <0.05. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics. The 224 patients ranged in age from 0.1 to 19.9 years (mean 14.5 ± 3.6 years) at ICD implantation for secondary (n = 36) or primary (n = 188) prevention (Fig. 1, Table 1). Of these patients, 134 (60%) were ≤15 years of age; 151 (67%) were male. The mean follow-up period was 4.3 ± 3.3 years (range to 17 years).

Appropriate ICD interventions. ALL PATIENTS. Of 224 study patients, 43 (19%) experienced ≥1 appropriate ICD intervention immediately restoring sinus rhythm by terminating VF (n = 21) or VT (n = 22) (Figs. 2 to 5). Initial ICD activations were defibrillation shocks in 40 patients and overdrive antitachycardia pacing in 3. The appropriate intervention rate for the overall study group was 4.5% per year (95% CI: 3.3% to 6.0%).

Patients with appropriate discharges underwent initial implantation at 13.5 ± 3.6 years of age (range: 4 to 19 years) and experienced first intervention at 16.4 ± 4.8 years (range: 5 to 26 years). Cumulative 5-year probability of discharge was 17%.

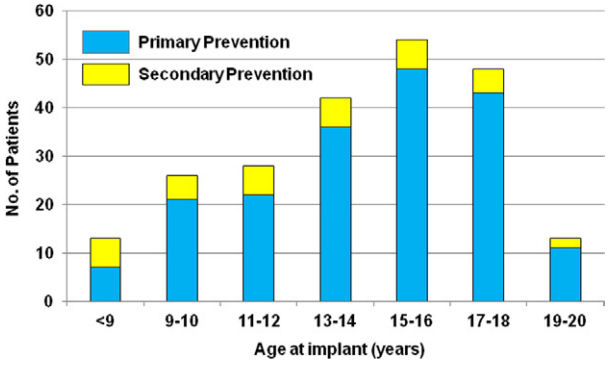

Figure 1 Patient Age at Defibrillator Implantation

Shown for 224 pediatric patients with hypertrophic cardiomyopathy judged at high risk for sudden death who underwent implantation for primary or secondary prevention.

SECONDARY PREVENTION. Thirty-six study patients received ICDs after resuscitated cardiac arrest or sustained VT; 17 (47%) experienced appropriate discharges at ages 5 to 26 years (mean 15.6 ± 6.4 years; at 14.0% per year; 95% CI: 7.7% to 22.7%). Cumulative 5-year probability of discharge was 43%. Of these 17 patients, 15 had no or only mild heart failure symptoms.

PRIMARY PREVENTION. Appropriate interventions occurred in 26 of 188 patients (14%) judged at increased risk for SD solely on the basis of risk markers. Initial events occurred at ages 9 to 23 years (mean 17.0 ± 3.4 years; at 3.1% per year; 95% CI: 2.0 to 4.4). Cumulative 5-year probability of discharge was 12%. Of these 26 patients, 22 had no or only mild heart failure symptoms. The rate of ICD intervention for secondary prevention exceeded that for primary prevention 4-fold (hazard ratio: 4.1; 95% CI: 2.2 to 7.5; p < 0.001) (Fig. 3).

Patients with appropriate interventions (n = 26) had greater magnitude of LVH than patients without interventions (n = 162) (30 ± 11 mm vs. 25 ± 9 mm, respectively, p = 0.026). Of the 43 patients who underwent surgical myectomy, 2 (5%) incurred appropriate interventions a mean of 0.2 ± 5.3 years later (rate 1% per year).

Timing and multiple shocks. Time between implantation and first appropriate ICD intervention ranged from 1 day to 8.6 years (mean 2.9 ± 2.7 years; ≥5 years in 13 patients [30%]) (Fig. 4). Twenty-five study patients received ≥2 total therapies (range to 7), including 13 who underwent implantation for primary and 12 for secondary prevention. ICD storms (≥2 shocks in 24 h) were reported in 8 others. Twenty-seven of 43 appropriate interventions occurred in the initial 30 months after implantation, including 12 (44%) in patients with ICDs implanted for secondary prevention or with end-stage systolic dysfunction.

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Table 1 Clinical, Echocardiographic, and Demographic Features in 224 Children and Adolescents With HCM Who Underwent ICD Implantation for Primary or Secondary Prevention

Characteristic	All Study Patients	Primary Prevention		Secondary Prevention	
		Overall	≥1 Appropriate Intervention	Overall	≥1 Appropriate Intervention
Number of patients	224	188	26	36§	17
Age at implantation (yrs)	14.5 ± 3.6	14.7 ± 3.5*	14.0 ± 2.7†	12.9 ± 4.4	12.9 ± 4.5
Age at first ICD intervention (yrs)	16.4 ± 4.8	—	17.0 ± 3.4	—	15.6 ± 6.4
Male	151 (67%)	124 (66%)	16 (62%)†	27 (75%)	12 (71%)
Follow-up duration (yrs)	4.3 ± 3.3	4.5 ± 3.3*	3.0 ± 2.7	3.5 ± 3.4	2.7 ± 2.7
NYHA class at implantation					
I	159 (71%)	126 (67%)	20 (77%)†	33 (92%)	16 (94%)
II	49 (22%)	46 (24%)*	3 (12%)†	3 (8%)	1 (6%)
III/IV	16 (7%)	16 (9%)*	3 (12%)†	0	0
NYHA class at last evaluation					
I	159 (71%)	133 (71%)	18 (69%)	26 (72%)	9 (53%)
II	47 (21%)	39 (21%)	6 (23%)	8 (19%)	6 (35%)
III/IV	18 (8%)	16 (9%)	2 (8%)	2 (6%)	2 (12%)
Maximal LV wall thickness (mm)	25.5 ± 9.8	26.0 ± 9.3	29.8 ± 11.4‡	22.7 ± 11.8	21.5 ± 9.4
LV end-diastolic dimension (mm)	40.2 ± 8.8	40.5 ± 8.6	41.8 ± 15.2†	38.7 ± 9.7	39.5 ± 10.5
Left atrial dimension (mm)	37.8 ± 9.2	37.9 ± 9.1	37.5 ± 9.8†	37.6 ± 9.8	34.5 ± 9.8
LV outflow gradient at rest					
>30 mm Hg	54 (24%)	48 (26%)	10 (38%)†	6 (17%)	3 (18%)
<30 mm Hg	170 (76%)	140 (74%)	16 (62%)	30 (83%)	14 (82%)
Cardioactive medications at implantation	158 (71%)	135 (72%)	21 (81%)	23 (64%)	11 (65%)
Cardioactive medications at first appropriate intervention	36 (84%)	—	21 (81%)	—	15 (88%)
Ejection fraction < 50%	9 (4%)	5 (3%)	1 (4%)	4 (11%)	3 (8%)

Values are mean ± SD or n (%). *Significant difference versus secondary prevention ($p < 0.01$). †Variables unassociated with the likelihood of a primary prevention ICD appropriate intervention ($p = 0.054$ to 0.83). ‡Significant difference versus secondary prevention appropriate interventions ($p = 0.017$). §Includes 10 patients with extreme LV hypertrophy with wall thicknesses ≥ 30 mm, of whom 4 had appropriate ICD shocks.

HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricular; NYHA= New York Heart Association.

Drugs. Of 43 patients with appropriate interventions, 36 (84%) were taking ≥1 cardioactive medications at first ICD intervention: beta-blockers (n = 31), calcium-channel blockers (n = 5), amiodarone (n = 2), or disopyramide (n = 1).

Clinical outcomes. SYMPTOMS. At implantation, 159 patients (71%) were asymptomatic, 49 (22%) had mild heart failure symptoms (New York Heart Association class II), and 16 (7%) were severely symptomatic (class III). At the most recent evaluation, 30 of 159 initially asymptomatic patients progressed to class II (n = 23) or class III (n = 7, including 3 with advanced end-stage [ejection fraction < 50%] heart failure) (20); 10 of these 30 patients experienced appropriate interventions.

MORTALITY. During follow-up, 216 of 224 patients (96%) survived, including 41 who underwent surgical myectomy, 1 who had alcohol ablation, and 4 who underwent heart transplantation. Eight patients (4%) died, 3 from post-transplantation complications, 1 from progressive heart failure while awaiting transplantation, and 1 after postoperative myectomy; 1 patient died suddenly when a defective ICD failed to defibrillate a lethal arrhythmia (21). Two other patients who underwent implantation after cardiac arrest subsequently died of multisystem disease and anoxic encephalopathy. Therefore, of the 224 patients, 54 (24%) were judged to have early, severe disease expression (mean age 19 ± 5.7 years), leading to heart failure, surgical myectomy, heart transplantation, or death.

Risk factor analysis. NUMBER OF RISK FACTORS. Among 188 primary prevention patients, ICDs were implanted on the basis of 1 (n = 88), 2 (n = 71), or ≥3 (n = 29) risk markers (Table 2). ICD interventions occurred in the same proportion for patients who underwent implantation for 1 (12 of 88 [14%]), 2 (10 of 71 [14%]), or ≥3 (4 of 29 [14%]) risk factors ($p = 1.00$) (Fig. 5); intervention rates per 100 person-years were 3.1, 2.9, and 3.8, respectively ($p = 0.16$).

SPECIFIC RISK FACTOR. The most common markers associated with prophylactic implantation decisions were extreme LVH (n = 117 [62%]), family history of HCM-related SD (n = 78 [41%]), and unexplained syncope (n = 71 [38%]). Of 26 primary prevention interventions, the most common marker identified (alone or in combination) was extreme LVH (17 of 26 [65%]), while 13 other patients (50%) had unexplained syncope and 10 (38%) had family histories of HCM-related SD; less common markers were nonsustained VT and exercise hypotensive blood pressure response (both 3 of 26 [12%]) ($p = 0.002$) (Fig. 6).

Of 88 patients who underwent implantation specifically for a single risk marker, appropriate ICD interventions occurred in 5 of 37 (14%) for extreme LVH, 4 of 33 (12%) for family

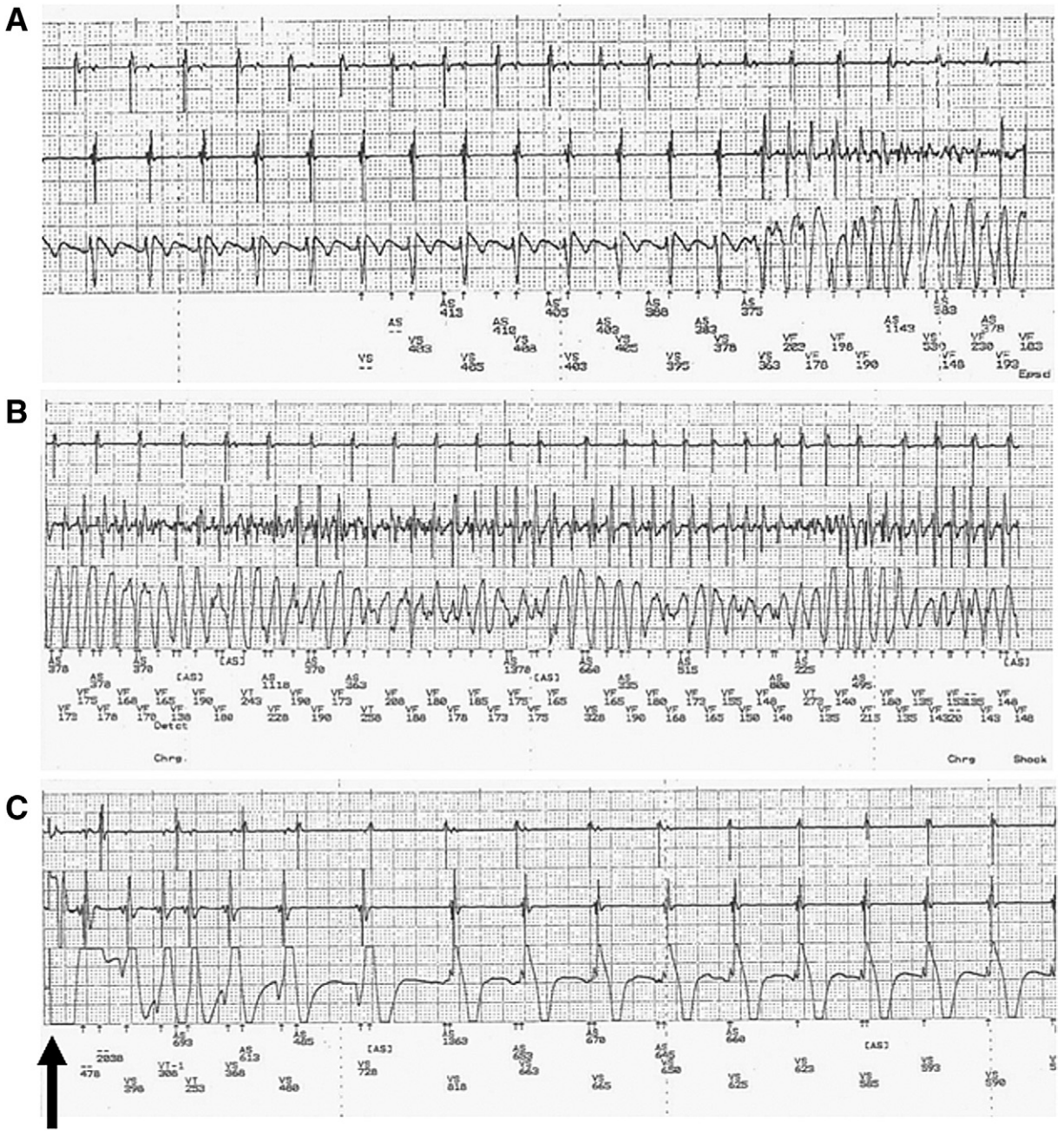

Figure 2 **Appropriate Implantable Cardioverter-Defibrillator Shock in Patient With Hypertrophic Cardiomyopathy**

Stored intracardiac ventricular electrograms from an asymptomatic 16-year-old male patient who underwent implantation for primary prevention of sudden death (age 15 years). Event occurred 10 months after implantation during a physical altercation. **(A)** After period of sinus rhythm, ventricular fibrillation (VF) intervenes abruptly; **(B)** VF continues; **(C)** defibrillator discharges appropriately with a 31-J shock, restoring sinus rhythm. Continuous tracing recorded **left to right in each panel**.

history of SD, and 3 of 13 (23%) with syncope; 2 other implants were for nonconventional indications (Table 2).

Complications. Sixty-three patients (28%; 6.5% per year) experienced inappropriate ICD shocks due to sinus tachycardia (n = 30), supraventricular tachycardia (n = 12), T-wave oversensing (n = 12), lead malfunction (n = 7), or electrical interference (n = 2). Inappropriate shocks occurred with similar frequency in patients who underwent implantation for primary (52 of 188 [28%]) versus secondary (11 of 36 [31%]) prevention (p = 0.72), those taking cardioactive medications at implantation (42 of 156 [27%]) versus those not taking drugs (21 of 68 [31%]) (p = 0.55), and those who underwent implantation at ≤15 years of age (36 of 134 [27%]) versus >15 years of age (27 of 90 [30%])

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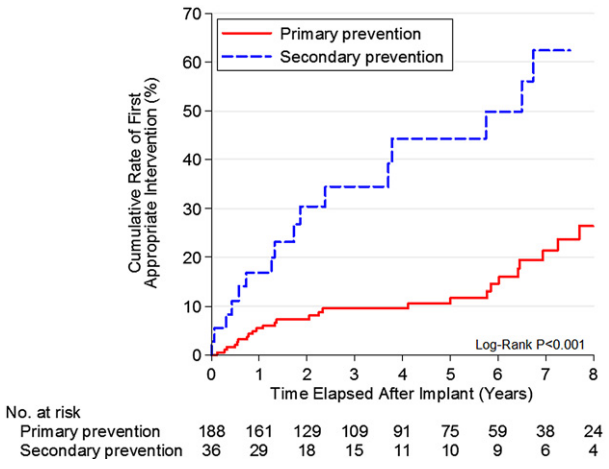

Figure 3 ICD Intervention Rates

Cumulative rates for first appropriate implantable cardioverter-defibrillator (ICD) intervention, shown separately for patients who underwent implantation for primary (n = 188) or secondary (n = 36) prevention. The rate of first appropriate ICD shock for secondary prevention exceeded that for primary prevention by 4-fold.

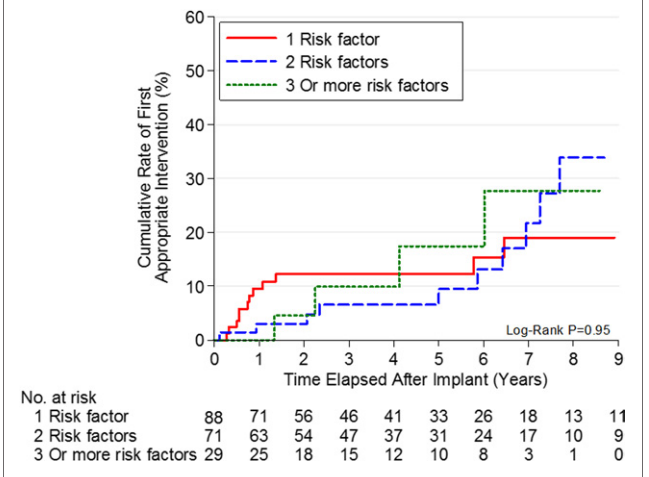

Figure 5 Number of Sudden Death Risk Factors and ICD Interventions

Cumulative rates for first appropriate implantable cardioverter-defibrillator (ICD) intervention in 188 patients who underwent implantation for primary prevention and 1, 2, or ≥3 risk markers. Event distribution was nonuniform during the follow-up period, with early interventions disproportionate (p = 0.023).

(p = 0.61). Notably, of 63 patients experiencing inappropriate shocks, 19 (30%) also had appropriate interventions.

An additional 28 study patients (12%) had complications regarded as particularly significant: lead fracture, dislodgement, or insulation failure without inappropriate shocks (n = 15); infection (n = 2); hemorrhage or thrombosis (n = 4); generator malfunction (n = 4); and right ventricular perforation, lacerated coronary vein, or exploratory sternotomy (n = 1 each). Therefore, 91 patients (40%) experienced ≥1 device-related complication (9.5% per year) at a mean age of 17 ± 5 years.

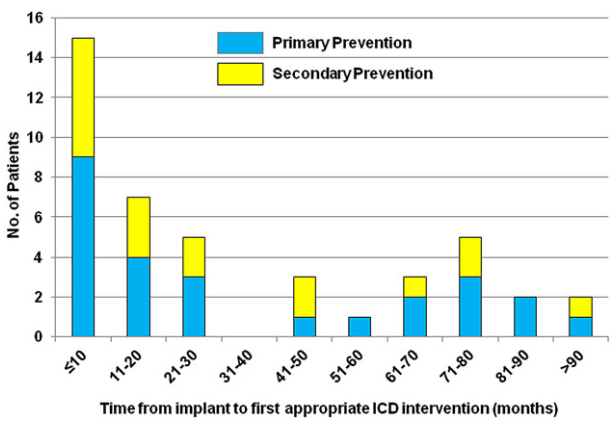

Figure 4 Unpredictability of Arrhythmogenic Substrate in Patients With Hypertrophic Cardiomyopathy

Time intervals from implantable cardioverter-defibrillator (ICD) implantation to first appropriate intervention in 224 patients.

Discussion

The prevention of SD is a major aspiration for the HCM population (1,3,4). Over the past decade, studies documenting the frequency of ICD interventions terminating potentially lethal tachyarrhythmias, largely in adult patients undergoing implantation for high-risk status, have reported the lifesaving potential of this contemporary therapy (3,4,8,22–26). Indeed, ICDs have changed the natural history of HCM for many patients and remain the only treatment strategy that prolongs life in patients with this disease. In our previous large, primarily adult registry (3,4), patients who underwent implantation at an average age of 42 years had a 5% per year intervention rate (primary prevention 4% per year). These favorable results have been replicated in several smaller series reporting virtually identical discharge rates (8,22–26).

Although ICD experience in HCM has been predominantly in adult patients, SD has an important predilection for younger patients (27). To clarify the role of ICD therapy in children and adolescents, we assembled the present unique multicenter international cohort of high-risk patients with HCM who underwent implantation at <20 years of age. In this study of >200 pediatric patients, ICDs proved effective in aborting life-threatening VT or VF in almost 20% (about 90% of these with no or only mild symptoms).

The secondary prevention annual intervention rate was 13% for those patients surviving cardiac arrest and about 3% for primary prevention on the basis of risk factors, and similar to rates previously reported for high-risk adult patients with HCM (1,3,4). When extrapolated, this rate predicts a substantial ICD intervention rate over the many

Table 2 Primary Prevention Risk Factors and ICD Interventions in 188 High-Risk Children and Adolescents

Primary Prevention Risk Factor	N (%) of 188 Patients Undergoing Implantation§	N (%) With Appropriate Discharges	1 Risk Factor Only, N (%) With Appropriate Discharges	N (%) of 26 Appropriate Discharges†
Extreme LVH	117 (62%)	17/117 (15%)†	5/37 (14%)‖	17 (65%)
Syncope	71 (38%)	13/71 (18%)	3/13 (23%)	13 (50%)
Family history HCM-related SCD	78 (41%)	10/78 (13%)	4/33 (12%)	10 (38%)
Hypotensive BP response to exercise	33 (18%)	3/33 (9%)	0/1	3 (12%)
NSVT	22 (12%)	3/22 (14%)	0/2	3 (12%)
Other*	2 (1%)	0	0/2	0

*Implantations for nonstandard indications, including 1 patient each with end-stage and systolic dysfunction (ejection fraction < 50%), age 19 years, and Wolff-Parkinson-White syndrome with induced atrial fibrillation leading to ventricular fibrillation during programmed stimulation. †Of the 17 patients with appropriate interventions for extreme LVH, wall thicknesses were ≥30 mm in 15 (range: 30 to 51 mm), and *z*-scores were 16 and 17 in the 2 patients with absolute thicknesses < 30 mm (27 mm at 15 years and 21 mm at 9 years, respectively). ‡$p = 0.002$, comparing the likelihood of appropriate interventions with respect to risk factors. §Each of the 188 patients had ≥3 risk markers tested, 73 patients had 4 markers tested, and 83 had all 5 markers tested. ‖Maximum left ventricular wall thicknesses were ≥30 mm in 4 of the 5 patients (30, 38, 42, and 44 mm; age at implantation 5 to 15 years) and 27 mm in 1 patient.

BP = blood pressure; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death. Other abbreviations as in Table 1.

years that these young patients will continue to be at risk. Indeed, the interval from implantation to first device activation can be considerable, up to 10 years in adults (1,3,4,22), and possibly even longer. In the present study, time from implantation to first appropriate discharge was up to 8 years and ≥5 years in about one-third of patients.

There is virtually no disagreement regarding the appropriateness of ICD therapy after cardiac arrest (secondary prevention) (1,3,9,10). The major issue influencing ICD decision making in children and adolescents is patient selection for primary prevention. Our data on the number of risk factors required to justify implant consideration proved consistent with the experience in adult patients (1,3,4,10,22). Specifically, we could not identify a significant difference in the likelihood of appropriate ICD discharges among patients who underwent implantation for 1, 2, or ≥3 conventional risk markers. That almost 50% of appropriate interventions were in patients with only 1 risk factor

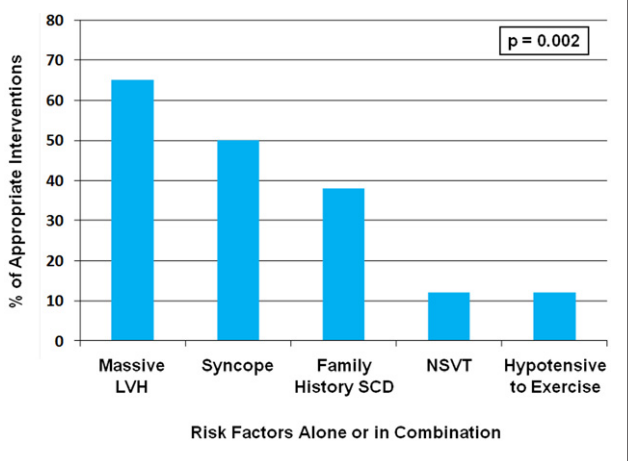

Figure 6 Distribution of Primary Prevention Risk Factors in Patients Who Experienced Appropriate Implantable Cardioverter-Defibrillator Interventions

Interventions were nonuniform in distribution with respect to risk factors ($p = 0.002$). LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death.

substantiates the principle that a single major marker within the clinical profile of an individual patient may be sufficient to consider a prophylactic ICD (1,3,4,22).

In this cohort, extreme LVH was the risk marker most commonly associated (either alone or in combination with other markers) with future ICD interventions i.e., extreme LVH was present in about two-thirds of patients experiencing appropriate discharges for primary prevention. This observation is consistent with the recognition that massive degrees of LVH were an important SD risk factor for patients with HCM in the pre-ICD era (13).

Furthermore, in this and other studies, ICDs proved effective in terminating VT and VF despite substantially increased LV mass and/or LV outflow obstruction with high intraventricular pressures. Notably, 4 of our 5 patients in whom extreme LVH was the sole risk factor promoting the implantation of prophylactic ICDs had LV wall thicknesses ≥30 mm, suggesting that the absolute 30-mm cutoff for high risk may be relevant to HCM children and adolescents independent of body size, similar to the circumstance in adults (13).

It was not possible to apply a Cox proportional hazards regression analysis to assess the relative strength of individual risk factors for ICD interventions because of insufficient power (maximum 0.1), given our relatively low event rate. Notably, ambulatory nonsustained VT (the only SD marker that directly measures arrhythmia burden in HCM) was uncommonly associated with events, in contrast to the HCM population data of Monserrat et al. (28). As a sole risk marker, the hypotensive blood pressure response to exercise is often problematic and is rarely the sole basis for primary prevention ICD decisions, given that it can be triggered by dynamic outflow obstruction and is potentially reversible by surgical myectomy (11).

At this early juncture, it is uncertain whether ICDs offer such very young, high-risk patients an opportunity to achieve normal or near-normal longevity, given the recognized unpredictability and complexity of this disease (1,3,4,22,29). However, notably, ICDs failed to abort an SD event in only 1 study patient, a high-risk 21-year-old

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male patient with preserved systolic function who died because his mechanically defective ICD (known only to the manufacturer) failed to deliver a defibrillation shock because of massive electrical overstress and short circuiting (21).

Patients were entered into the present cohort because they were judged to be at high risk for SD by their managing cardiologists. Therefore, our observations are confined to a particular subset of patients that may not be entirely representative of the general HCM population of this age, for which the vast majority do not experience life-threatening events. Indeed, 25% of our patients experienced early-onset aggressive disease (including heart transplantation), which in principle overwhelmed the potential benefit of ICD implantation.

The importance of device-related complications cannot be underestimated or overstated in this young patient cohort. A significant minority of patients experienced adverse ICD consequences, including lead malfunction (sometimes due to manufacturing defects), inappropriate shocks, and other more substantial complications. In particular, lead systems continue to constitute the "weakest link" in the ICD system and may not be designed to remain intact and perform effectively over the very long periods required for young patients and HCM and decades of productive life ahead (30). Therefore, ICD decisions in children inevitably require weighing anticipated benefit for SD prevention and the preservation of life against possible device complications, requirement for multiple generator changes, the possible psychological burden imposed by ICDs, and some quality-of-life restrictions (31). Indeed, the complication rate (including inappropriate shocks) was 3-fold higher than appropriate interventions for VT or VF (9% vs. 3%). However, importantly, about 30% of patients with device complications also had appropriate lifesaving ICD interventions.

These considerations can create unique management dilemmas in pediatric cardiology, particularly when decisions regarding prophylactic implants involve ambiguous risk-factor assessment. Indeed, the paradox emerges in which healthy-appearing children and adolescents in the age range of greatest SD predilection (27) are also those most likely to experience device complications, given their youth and level of physical activity.

Whether subcutaneous defibrillators, largely untested in HCM, will ultimately prove as efficacious as transvenous systems is not yet known (32,33). However, at present, caution is warranted in considering subcutaneous defibrillators in this young patient population (33). Single-chamber ICDs still represent the most appropriate option for young high-risk patients with HCM, given the lower potential for lead complications than is expected with dual-chamber devices (34).

The disproportionate occurrence of relatively early defibrillation shocks suggests the theoretical possibility of lead-related proarrhythmia (35), rather than beneficial disease-related interventions. However, in this study, as in our registry of adult patients with HCM (36), a substantial proportion of early ICD discharges could be explained by a subset of patients particularly prone to subsequent VT or VF because they underwent implantation after cardiac arrest or with systolic dysfunction. In addition, it is theoretically possible that some defibrillator shocks considered to be appropriate therapy could have been triggered by ventricular tachyarrhythmias that may have self-terminated (i.e., if the device had not been present), similar to the situation that has been proposed for implanted patients with ischemic heart disease (37,38). However, whether the principle in coronary artery disease that ICD interventions for VT overestimate appropriate device therapy (and SD rates) should be applied directly to HCM is presently unresolved.

Our registry study design was unavoidable, given the impracticality of prospective and/or randomized ICD trials in HCM, particularly in this age group. Obstacles to randomization include the infrequency of clinically identified patients with HCM in pediatric cardiology practice, the relatively low event rate dispersed over many decades, and ethical considerations whereby some patients would be excluded from potentially lifesaving therapy. Therefore, the selection of patients for ICDs was based on current risk-factor models (1) and practice patterns instituted at each participating center, with decision-making consistent with the available consensus recommendations in the vast majority of patients (3,4,9,10,22).

Conclusions

Data from this large, international, multicenter cohort are relevant to patient management and ICD decision making in young high-risk patients with HCM. Our findings support the current risk stratification strategy for identifying patients with HCM susceptible to life-threatening ventricular tachyarrhythmias, and underscore an important role for SD prevention (with ICDs) in children and adolescents. These data also emphasize the importance of balancing considerations for the preservation of life using ICDs against the possibility of device-related complications that may be anticipated with implantation so early in life.

Acknowledgments

As always, the authors thank Michel Mirowski, MD, and Morton M. Mower, MD, for their pioneering work in conceptualizing and creating the ICD for patients with life-threatening cardiac disease.

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Key Words: cardiomyopathy ■ children ■ defibrillators ■ sudden death ■ ventricular fibrillation.

APPENDIX

For a list of participating centers and investigators, please see the online version of this article.