Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Clinical Course and Quality of Life in High-Risk Patients With Hypertrophic Cardiomyopathy and Implantable Cardioverter-Defibrillators

BACKGROUND: High-risk patients with hypertrophic cardiomyopathy (HCM) are identified by contemporary risk stratification and effectively treated with implantable cardioverter-defibrillators (ICDs). However, long-term HCM clinical course after ICD therapy for ventricular tachyarrhythmias is incompletely understood.

METHODS AND RESULTS: Cohort of 486 high-risk HCM patients with ICDs was assembled from 8 international centers. Clinical course and device interventions were addressed, and survey questionnaires assessed patient anxiety level and psychological well-being related to ICD therapy. Of 486 patients, 94 (19%) experienced appropriate ICD interventions terminating ventricular tachycardia/ventricular fibrillation, 3.7% per year for primary prevention, over 6.4±4.7 years. Of 94 patients, 87 were asymptomatic or only mildly symptomatic at the time of appropriate ICD interventions; 74 of these 87 (85%) remained in classes I/II without significant change in clinical status over the subsequent 5.9±4.9 years (up to 22). Among the 94 patients, there was one sudden death (caused by device failure; 1.1%); 3 patients died from other HCM-related processes unrelated to arrhythmic risk (eg, end-stage heart failure). Post-ICD intervention, freedom from HCM mortality was 100%, 97%, and 92% at 1, 5, and 10 years, distinctly lower than in ischemic or nonischemic cardiomyopathy ICD trials. HCM patients with ICD interventions reported heightened anxiety in expectation of future shocks, but with intact general psychological well-being and quality of life.

CONCLUSIONS: In HCM, unlike ischemic heart disease, prevention of sudden death with ICD therapy is unassociated with significant increase in cardiovascular morbidity or mortality, or transformation to heart failure deterioration. ICD therapy does not substantially impair overall psychological and physical well-being.

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Key Words: cardiomyopathy, hypertrophic ■ death, heart failure ■ death, sudden ■ defibrillators ■ psychology ■ ventricular fibrillation ■ ventricular tachycardia

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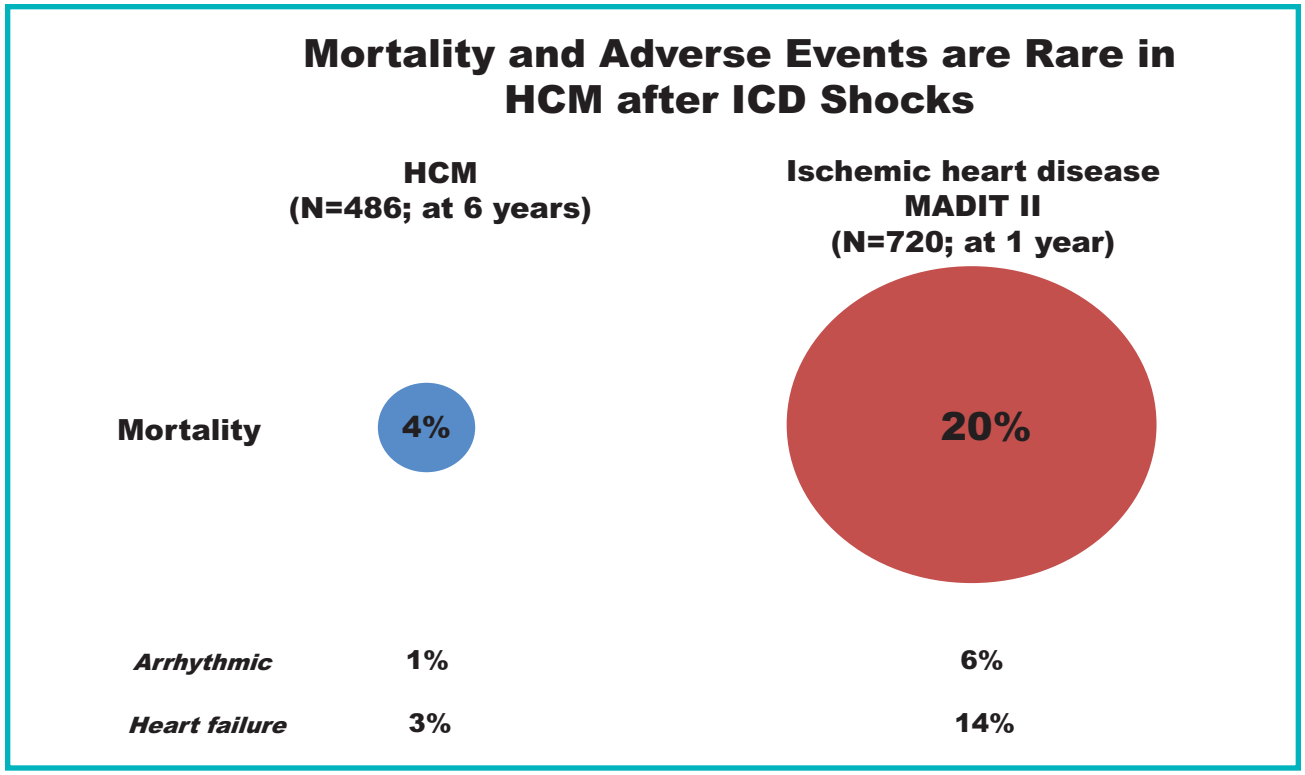

WHAT IS KNOWN?

- In hypertrophic cardiomyopathy, the implantable defibrillator has become a highly effective therapy for terminating ventricular tachyarrhythmias and preventing sudden death.
- Clinical course after an appropriate device intervention is not known.

WHAT THE STUDY ADDS?

- In contrast to experience with ischemic heart disease, defibrillator interventions in patients with hypertrophic cardiomyopathy are not followed by an increase in cardiovascular morbidity or mortality caused by heart failure deterioration or sudden death.
- Device therapy in hypertrophic cardiomyopathy does not significantly impair overall psychological well-being or quality of life.

In hypertrophic cardiomyopathy (HCM), the risk of sudden cardiac death in young people caused by ventricular tachyarrhythmias has been a highly visible complication of this heterogeneous disease.[1] The implantable cardioverter-defibrillator (ICD) is now established as a fundamental therapy for prevention of sudden death in this patient population, independent of age, and based on a series of multicenter studies and meta-analyses over the past >15 years.[1–11]

Nevertheless, a remaining question is whether ICD interventions that terminate ventricular tachycardia/ventricular fibrillation (VT/VF) trigger deterioration in clinical course or impairment in quality of life (including psychological). Therefore, to address whether long-term clinical course and mortality risk subsequent to termination of life-threatening arrhythmias is distinctive in HCM, we have assembled a large multicenter international cohort of high-risk HCM patients with ICDs.

METHODS

Patient Population

The study group enrolled 486 patients with HCM, aged 51±16 years, who had received ICDs for high-risk status at 8 international referral institutions for this disease in the United States, Europe, and Australia. The cohort comprised all consenting HCM patients at each participating center with an ICD implanted for either primary (n=437) or secondary (n=49) prevention between 2001 and 2015. Age at ICD implantation was 44±16 years.

Decisions regarding the appropriateness of ICD implantation were made according to customary clinical practice by managing cardiovascular specialists at each participating center, on a case-by-case basis, and with the guidance of the risk stratification model advanced in the 2011 US/Canada ACC/AHA consensus recommendations for the management of HCM.[10]

Diagnosis

Each patient had an unequivocal clinical diagnosis of HCM based on 2-dimensional echocardiogram and cardiovascular magnetic

resonance demonstration of a hypertrophied and nondilated left ventricle (LV) in the absence of another cardiac or systemic disease that could account for the magnitude of hypertrophy evident.[10] Patients with known phenocopies of HCM (eg, Fabry disease, LAMP2 [lysosome-associated membrane protein-2] cardiomyopathy, or amyloidosis) were excluded.

This study was reviewed and approved by the institutional review boards (or the equivalent) at each participating institution, including Allina Health System. Patient participants in this study provided written and oral informed consent permitting use of patient medical information for research.

Implantable Cardioverter-Defibrillators

Each study patient received a single- or dual-chamber ICD capable of antitachycardia and antibradycardia pacing. Expert electrophysiologists at each center analyzed stored intracardiac electrograms for arrhythmias responsible for defibrillator discharges, according to prior published definitions.[6] Device discharges, either defibrillation shocks (n=64) or antitachycardia pacing (n=30) were considered appropriate when triggered by ventricular fibrillation or rapid sustained ventricular tachycardia (rate ≥200/min). Rate cutoffs for arrhythmia detection were programmed and antitachycardia pacing activated at the discretion of the responsible electrophysiologist. Inappropriate interventions were triggered by heart rates exceeding the programmed threshold, as a consequence of supraventricular tachyarrhythmias, sinus tachycardia, or device or lead malfunctions.

Psychological Profiles

Patients were recruited to complete 3 personal surveys examining both ICD-specific adjustment and general psychological well-being and quality of life. Comparisons between patients who did (or did not) experience discharges from their ICDs were made.

Of the 486 patients, 250 (51%) completed a total of 720 surveys either at the time of a clinical visit or alternatively after receiving the questionnaire in the mail. Of these 250 patients, 89 (36%) had either an appropriate or inappropriate ICD intervention before enrollment in the survey section of the study. The patient-reported outcome measures used in this study were as follows:

Florida Shock Anxiety Scale

This scale is a validated and reliable measure of ICD shock–related anxiety, specifically with respect to the fear of triggering a shock (particularly with exercise) and the consequences of a device discharge, which includes cognitive, behavioral, emotional, and social impact.[12–14] The Florida Shock Anxiety Scale (FSAS) survey consists of 10 items that respondents rate on a 5-point scale from 1 to 5. Higher values represent greater shock anxiety. The total FSAS score is determined by summing the items. The FSAS is more specific for detecting anxiety related to cardiac disease and device management than the more general Hospital Anxiety and Depression Scale (HADS) and SF12 v.2 surveys.

Hospital Anxiety and Depression Scale

This survey incorporates separate anxiety and depression subscales and is a widely used and validated screening instrument to measure symptoms of anxiety and depression in people with physical health problems.[15,16] Each subscale (ie, anxiety or depression) includes 7 items (total of 14) with each item scored on a 0 to 3 scale. A score ≥8 on either subscale is consistent with increased symptoms of anxiety or depression.

SF12 v.2 Health Survey

This survey uses a short form (12 questions) to measure general functional health status and well-being (physical and mental).[17]

Statistical Analysis

Data are expressed as mean±SD for continuous variables, and proportions for categorical variables. Student *t* test or Wilcoxon rank-sum tests addressed the statistical significance of continuous variables, and χ^2 or Fisher exact test analyzed categorical variables, as appropriate.

Follow-up duration was from device implantation to the time of first appropriate ICD discharge. In patients without an ICD intervention, follow-up was taken to most recent evaluation (or death). Follow-up period was 6.4±4.7 years for the overall study group.

Rates of first appropriate intervention were computed as the ratio between the number of events observed and the sum of person-years accumulated during the follow-up period; 95% confidence intervals (CI) were calculated assuming a Poisson distribution of rare events. Time-to-event analyses were performed using the Kaplan–Meier method. Patients lost to follow-up were censored at the date of last clinical contact. Statistical computations were performed with Stata (version 11.2; STATA Corp, College Station, TX). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, on the basis of prior agreed-upon guidelines for patient confidentiality.

RESULTS

Baseline Clinical Characteristics

The 486 study patients were 44±16 years of age (range, 7–84) at device implant for primary or secondary prevention; 296 (61%) were male. Of the 486 patients, 272 (56%) were asymptomatic in New York Heart Association (NYHA) class I, 164 (34%) were mildly symptomatic in class II, and 50 (10%) were severely symptomatic in classes III/IV. Ventricular septal thickness was 23.6±7 mm with 109 patients (22%) ≥30 mm. LV end-diastolic dimension was 44±8 mm, and left atrial dimension was 44±9 mm.

ICD Interventions

Of the 486 patients, 94 (19%) experienced ≥1 appropriate primary (n=76) or secondary (n=18) prevention ICD discharge to terminate VT/VF. Event rate was 10.2% per year (95% CI, 6–16) for secondary prevention, and 3.7% per year (95% CI, 3.0–4.5) for primary prevention with cumulative 5-year probability of discharge 17.4% per year. Time interval from ICD implant to first appropriate inter-

vention was 3.5±3.3 years. Of the 94 patients with device discharges, 44 had >1 shock over follow-up, including 6 patients with VT storm episodes (≥3 shocks per 24 hours).

The numbers of risk factors in patients with appropriate primary prevention ICD interventions were 1 (43 patients), 2 (22 patients), and 3 to 4 (11 patients). Specific markers were nonsustained VT (n=45); family history of HCM-related sudden death (n=35); unexplained syncope (n=26); LV thickness ≥30 mm (n=22); extensive late gadolinium enhancement by CMR (n=18); hypotensive blood pressure response to exercise (n=11); and LV apical aneurysm (n=2). Ejection fraction in the 94 patients was 61±11%.

Inappropriate ICD shocks occurred in 96 patients (20%), at a rate of 2.1% per year, including 29 who also had appropriate device interventions. Of these 29 patients, 16 experienced an inappropriate shock first, 9 had appropriate interventions first, and 4 patients had both on the same day. Other reported complications included lead fracture (n=17), venous thrombosis (n=5); infection (n=5).

Symptomatic Status After ICD Interventions

Of the 94 patients with appropriate interventions, 87 had no or only mild heart failure symptoms (NYHA classes I or II) at the time of implant (Figure 1). After 5.9±4.9-year follow-up and after device discharge to interrupt VT/VF, 74 of the 87 patients (85%) remained asymptomatic (n=48) or with only mild symptoms (NYHA II; n=26). The other 13 patients (15%) developed progressive symptoms (to NYHA class III/IV), attributable to nonarrhythmic causes for which the ICD is not designed to protect against: for example, end-stage heart failure with systolic dysfunction leading to consideration for heart transplant[18] (n=6); permanent atrial fibrillation (n=3); LV outflow obstruction requiring myectomy or alcohol septal ablation (n=2); or comorbidity (n=2). At the end of follow-up, patients with or without appropriate ICD interventions did not differ with respect to the degree of heart failure symptoms (NYHA classes I/II: 77 [82%] versus 331 [85%]; *P*=0.41).

Mortality After ICD Interventions

There have been 7 deaths among the 94 patients with appropriate ICD interventions for primary and secondary prevention (Figure 2). Of these, only one was sudden and arrhythmic, occurring in an asymptomatic 22-year-old woman with massive LV hypertrophy who died of intractable ventricular tachyarrhythmias 5.9 years after an initial ICD shock when her defibrillator failed to restore sinus rhythm caused by a mechanically defective (St. Jude) lead.

Of the other 6 deaths, 3 were related to HCM and caused by end-stage heart failure[18] in NYHA classes III/IV at ages 54, 56, and 71 years: 7.3, 9.0, and 11.6 years after the first appropriate ICD intervention. One patient died of chronic obstructive pulmonary disease and pulmonary hypertension at 85 years of age, 2.5 years after

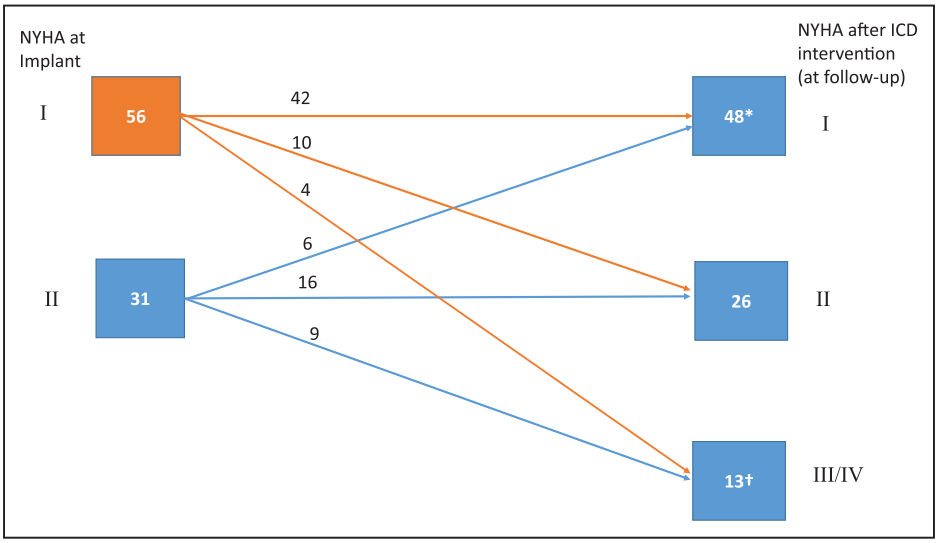

Figure 1. Diagrammatic representation of New York Heart Association (NYHA) functional status before and after appropriate implantable cardioverter-defibrillator (ICD) interventions for ventricular tachycardia/ventricular fibrillation confined to the 87 study patients with no or only mild heart failure symptoms at the time of implant.
Seven other patients, not shown here, were already severely symptomatic in NYHA class III at ICD implant and study entry with end-stage heart failure (n=3), left ventricular (LV) outflow obstruction (n=2), and comorbidities (n=2). *Sudden death caused by device failure in 22 y old with massive LV hypertrophy. †Symptom progression because of nonarrhythmic or non-HCM causes: end-stage heart failure (n=6, including 3 deaths), permanent atrial fibrillation (n=3); LV outflow obstruction (n=2); and comorbidity (n=2).

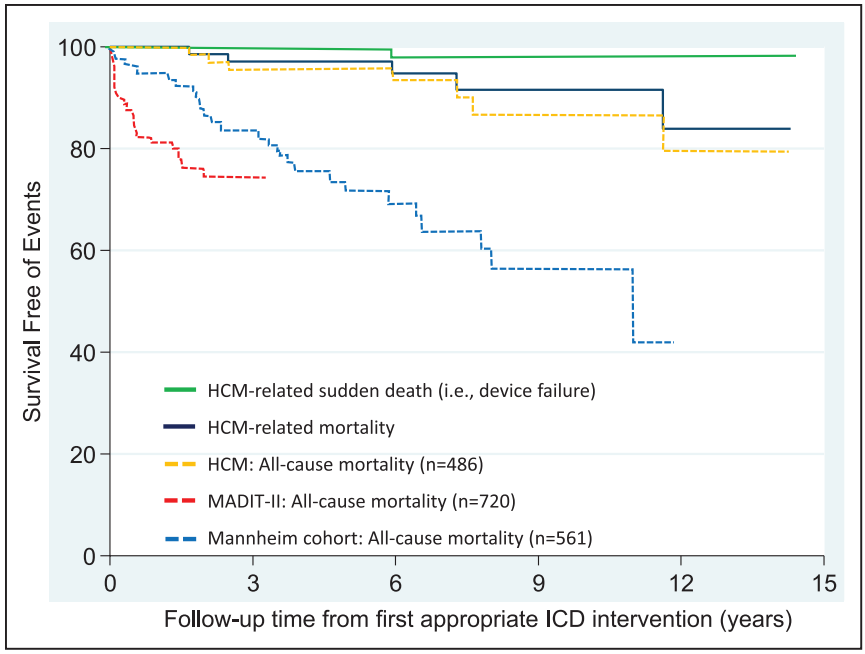

Figure 2. Kaplan–Meier survival curves comparing total (all-cause) or hypertrophic cardiomyopathy (HCM)–related mortality after the first implantable cardioverter-defibrillator (ICD) intervention. Data taken from present HCM study patients and from patients reported in MADIT II (Multicenter Automatic Defibrillator Implantation Trial II)[19,20] and Mannheim defibrillation trial.[22]

the first ICD intervention, and 2 others already in NYHA class III at implant died of noncardiac causes (cancer; ages 46 and 58 years): 2 and 8 years after first ICD intervention.

Survival Analyses

Of the 94 patients with appropriate device interventions, freedom from sudden death at 1, 5, and 10 years was 100%, 100%, and 98% (95% CI, 85–99), respectively. Freedom from HCM-related mortality at 1, 5, and 10 years was 100%, 97% (95% CI, 89–99), and 92% (95% CI, 77–97), respectively. Freedom from all-cause mortality at 1, 5, and 10 years was 100%, 96% (95% CI, 87–98), and 87% (95% CI, 72–94), respectively.

We compared post-ICD shock survival in the present HCM study patients with that in ischemic and dilated cardiomyopathy reported in 3 selected randomized trials for which these specific data are available, that is, the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II),[19,20] the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),[21] and the Mannheim trial.[22] After ICD interventions, survival free of sudden death, HCM-related death, and freedom from total (all cause) mortality in the present HCM series markedly exceeds that in each of the 3 non-HCM trials (Table 1).

Patient-Reported Psychological Outcomes

Florida Shock Anxiety Scale

Patients experiencing ICD interventions (appropriate or inappropriate) reported higher levels of shock anxiety

Table 1. Outcomes After ICD Interventions in HCM as Compared With Other Clinical Trials

	Present HCM Registry	MADIT II[18,19]	SCD HeFT[20]	Mannheim[21]
	Primary/secondary prevention	Post-MI; EF ≤30%	Ischemic/ nonischemic CM; EF ≤35%	Ischemic/ dilated CM; EF ≤35%
Cohort size	486	720	811	561
Follow-up, mo	42	21	46	49
Appropriate ICD interventions, n (%)	94 (19)	169 (23)	182 (22)	74 (13)
Deaths after appropriate ICD interventions, n (%)	7 (7)*	29 (17)	67 (37)	27 (36)
1-y mortality rate, %	0	20	24	5
5-y mortality rate, %	4	N/A	N/A	25

CM indicates cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; MADIT II, Multicenter Automatic Defibrillator Implantation Trial II; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; and SCD HeFT, Sudden Cardiac Death in Heart Failure Trial.

*Four deaths were HCM-related and 3 deaths were cardiac but non-HCM related or caused by comorbidities.

than did patients who were free of device interventions (total scores 17.4±6.7 versus 15.9±6.2, respectively; *P*=0.05; Table 2). However, there was no difference in the level of anxiety experienced when patients with appropriate interventions (n=94) were compared with patients with inappropriate shocks or major device complications (n=92; *P*=0.39–0.89; Table I in the Data Supplement).

Notably, FSAS scores specifically in the 25 patients with multiple appropriate shocks were not increased compared with those patients with single interventions (17.4±7.3 versus 17.7±6.6; *P*=0.86) and also were similar to the 3 patients with defibrillator storms (20.0±8.7).

Hospital Anxiety and Depression Scale

There were no significant differences among the ICD patient subgroups, in terms of anxiety and depression. For example, patients with ICD interventions displayed no more overall impairment in psychological well-being than did patients without interventions (5.2±3.7 versus 5.5±3.9 respectively; *P*=0.51; Table 2). In addition, an individual patient analysis showed that only 20% of patients with appropriate shocks (13/63) had HADS scores consistent with an abnormal psychological profile (ie, ≥8).

SV12 v.2

There were no significant differences among the ICD patient subgroups in terms of general health status and well-being (Table 2). Patients with ICD interventions (either appropriate or inappropriate) demonstrated no differences using the mental and physical components of the survey.

Relation to Age, Sex, and NYHA Class

Both the FSAS and HADS anxiety scores showed a modest but statistically significant inverse relationship to age (*P*=0.06 and *P*=0.01), supporting greater sensitivity to device therapy in younger patients (Figures I and II in the Data Supplement). On average, for every 10-year increase in age, FSAS anxiety scores decreased by 0.49 points, and HADS scores decreased by 0.35 points.

HADS scores tended to be higher in women than in men (*P*=0.047), on average by 1 point. Also, HADS scores were significantly higher, by 1.4 and 1.9 points on average in NYHA classes II and III patients compared with class I patients (*P*=0.045 and *P*=0.006, respectively). Patients who did or did not complete questionnaire surveys showed no significant and relevant differences in a large number of demographic or clinical variables (Table II in the Data Supplement). Patients who completed surveys were more likely to have appropriate ICD interventions but were less frequently in NYHA class III at most recent evaluation.

DISCUSSION

In this study of almost 500 high-risk HCM patients, we have addressed several issues related to ICD therapy. First, data from our international multicenter HCM population reinforces the principle that device therapy is efficacious in terminating VT/VF, restoring sinus rhythm, and preventing sudden death.[1–11] As a result of this >15-year ICD initiative,[3,9] substantial numbers of patients prophylactically implanted with devices have survived with good quality of life. The data reported here are also consistent with our prior experience (and that of other investigators), albeit with a slightly lower ICD event rate, probably attributable to greater numbers of primary prevention devices implanted most recently as this therapy continues to penetrate into HCM practice.[23]

Perhaps, most importantly, we have demonstrated a fundamental principle for HCM of which the ICD has greater impact on the natural history of HCM than in non-HCM diseases such as ischemic heart disease or other cardiomyopathies, perhaps not generally appreciated in the practicing cardiovascular community.

Older and clinically compromised ICD populations with heart failure and systolic dysfunction have been the subject of several large multicenter, prospective, and randomized trials substantiating the efficacy of device therapy.[19–22,24–27] In these populations, clini-

Table 2. Relation of Patient Psychological Survey Scores to ICD Interventions

	Any ICD Intervention	No Intervention	*P* Value	Appropriate ICD Intervention*	Inappropriate ICD Intervention	*P* Value
FSAS (total score)	17.4±6.7	15.9±6.2	0.05	17.6±6.9	17.2±6.5	0.85
HADS anxiety	5.2±3.7	5.5±3.9	0.55	5.2±3.8	5.2±3.5	0.85
HADS depression	3.2±2.7	3.5±3.7	0.87	3.2±2.9	3.0±2.4	0.99
SF12 v.2 (physical)	48.7±7.7	47.2±9.5	0.43	48.2±8.7	49.6±5.9	0.65
SF12 v.2 (mental)	50.5±10.2	52.0±8.4	0.52	50.6±10.3	50.3±10.2	0.89

FSAS indicates Florida Shock Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; and ICD, implantable cardioverter-defibrillator.
*Includes 29 patients experiencing both appropriate and inappropriate ICD interventions.

cal course in just the first year after appropriate (or inappropriate) ICD interventions is complicated by considerable morbidity and mortality. For example, in MADIT II of patients with myocardial infarction and LV dysfunction, 1 year post-shock fully 20% had died and 30% required heart failure hospitalizations often as the consequence of cardiorenal dysfunction.[19,20] In SCD-HeFT[21] of patients with chronic heart failure caused by ischemic or nonischemic cardiomyopathy and ventricular dysfunction, the 1-year post-ICD shock mortality was 24%. Therefore, in both MADIT II[19,20] and SCD-HeFT,[21] ICD shocks identified patients with an increase in heart failure mortality risk and decreased survival. Although ICD therapy for VT/VF was successful, the reduction in sudden death was offset by a high frequency of heart failure and non-sudden cardiac death occurring after the first successful device intervention. It has been suggested that this unfavorable clinical course after device shocks in patients with ischemic heart disease and nonischemic cardiomyopathy may be, in part, the consequence of ICD-induced myocardial damage to hearts also with preexistent scarring.[28]

In striking contrast, in our younger and generally healthier HCM patients, we found little evidence of post-shock adversity with zero mortality over the first 2 years after initial ICD interventions and deaths from a variety of non-sudden HCM or non–HCM-related causes at <1% per year over the next decade. Specifically, ICD interventions were unassociated with increased sudden death risk, in that 3 of 4 HCM-related deaths were directly attributable to mechanisms independent of arrhythmic risk (and the intent of ICD therapy), principally an evolution to the end stage with diffuse myocardial scarring and LV remodeling leading to consideration for heart transplant.[18,29] The only exception was an avoidable sudden death 6 years after ICD intervention in a young patient left unprotected from intractable ventricular tachyarrhythmias by a mechanically defective lead system. Therefore, these data support an impact of the ICD on the natural history of HCM that greatly exceeds non-HCM diseases, a distinction perhaps not generally appreciated in the practicing cardiovascular community.

In this investigation, we also sought to understand the patient psychological experience and quality of life associated with life-saving ICD therapy in HCM.[30] To this purpose, we selected 3 standard questionnaire surveys to be completed by patients.[12–17] Not unexpectedly, the more ICD-specific FSAS survey found a modest association between device discharges and elevated levels of anxiety, presumably the fear and anticipation of future uncomfortable arrhythmia-triggered ICD interventions. However, the HADS subpanels and SF12 v.2 survey found little evidence of excessive impairment in general psychological well-being.

These survey-questionnaire data in HCM patients are similar to those reported for patients with ischemic heart disease and ICDs.[31] Our findings in HCM generally support the principle of patient satisfaction with the ICD initiative, focused on preservation of life in high-risk patients with this complex genetic disease.[1,3,4,6,8,9] Attention to patient concerns, and apprehension related to ICD shocks, could ultimately mitigate the modestly elevated levels of shock anxiety identified in this study.

There are several issues impacting our data related to the psychological state of patients with ICDs in this exploratory study that deserve mention. One-half of the study patients chose not to complete the psychological surveys, which could represent a source of bias and influence our interpretation of the data. Nevertheless, patients who did (or did not) complete surveys showed no measurable differences with regard to many clinical and demographic variables. Although it may have been potentially advantageous to assess levels of patient satisfaction and psychological status before and after VT/VF events, practicalities related to our study design unfortunately prohibited this particular analysis. Finally, we were only able to show a modest (although statistically significant) correlation between ICD discharges and elevated anxiety levels (probably in anticipation of future shocks), a relationship that should, therefore, be interpreted with some caution.

In conclusion, the present data extend our understanding beyond the reaffirmation that ICD therapy alters clinical course in HCM with the inherent power to prevent unexpected sudden cardiac death. We have, in addition, established an important principle that in HCM patients ICD therapy does not thereafter alter quality of life, and is not associated with increased risk for sudden death or progressive heart failure.

ARTICLE INFORMATION

Received August 31, 2017; accepted January 17, 2018.

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.117.005820/-/DC1.

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gone Medical Center (M.V.S., A.K.); Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy (I.O.); Atlantic Health Systems, Morristown Memorial Hospital and Medical Center, NJ (S.L.W.).

Sources of Funding

This study was supported, in part, by an investigator-initiated grant from Medtronic, Inc.

Disclosures

Dr Semsarian is the recipient of a National Health and Medical Research Council Practitioner Fellowship (#1059156).

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