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ORIGINAL INVESTIGATIONS

Hypertrophic Cardiomyopathy in Adulthood Associated With Low Cardiovascular Mortality With Contemporary Management Strategies

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ABSTRACT

BACKGROUND Hypertrophic cardiomyopathy (HCM) has been prominently associated with adverse disease complications, including sudden death or heart failure death and a generally adverse prognosis, with annual mortality rates of up to 6%.

OBJECTIVES This study determined whether recent advances in management strategy, including implantable cardioverter-defibrillators (ICDs), heart transplantation, or other therapeutic measures have significantly improved survival and the clinical course of adult HCM patients.

METHODS We addressed long-term outcomes in 1,000 consecutive adult HCM patients presenting at 30 to 59 years of age (mean 45 ± 8 years) over 7.2 ± 5.2 years of follow-up.

RESULTS Of 1,000 patients, 918 (92%) survived to 53 ± 9.2 years of age (range 32 to 80 years) with 91% experiencing no or only mild symptoms at last evaluation. HCM-related death occurred in 40 patients (4% [0.53%/year]) at 50 ± 10 years from the following events: progressive heart failure (n = 17); arrhythmic sudden death (SD) (n = 17); and embolic stroke (n = 2). In contrast, 56 other high-risk patients (5.6%) survived life-threatening events, most commonly with ICD interventions for ventricular tachyarrhythmias (n = 33) or heart transplantation for advanced heart failure (n = 18 [0.79%/year]). SD occurred in patients who declined ICD recommendations, had evaluations before application of prophylactic ICDs to HCM, or were without conventional risk factors. The 5- and 10-year survival rates (confined to HCM deaths) were 98% and 94%, respectively, not different from the expected all-cause mortality in the general U.S. population (p = 0.25). Multivariate independent predictors of adverse outcome were younger age at diagnosis, female sex, and increased left atrial dimension.

CONCLUSIONS In a large longitudinally assessed adult HCM cohort, we have demonstrated that contemporary management strategies and treatment interventions, including ICDs for SD prevention, have significantly altered the clinical course, now resulting in a low disease-related mortality rate of 0.5%/year and an opportunity for extended longevity. (J Am Coll Cardiol 2015;65:1915–28) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

NYHA = New York Heart Association

SD = sudden death

VF = ventricular fibrillation

VT = ventricular tachyarrhythmia

Hypertrophic cardiomyopathy (HCM) has been historically associated with substantial morbidity and mortality and impaired longevity due to sudden death (SD) and complications of heart failure (1-10). However, the previous 15 years have witnessed the emergence of innovative nonpharmacological cardiovascular management strategies for HCM patients, including an expanded risk stratification algorithm, use of implantable cardioverter-defibrillators (ICDs) for SD prevention, and advances in refractory heart failure therapies, including heart transplantation (11-19).

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Nevertheless, there is limited objective evidence available supporting a cardiovascular mortality benefit attributable to contemporary management options within established HCM cohorts, and some uncertainty may persist in the practicing community (10,20). Generally, in adult cardiovascular practice, patients between 30 and 59 years of age (midlife) with HCM constitute the subgroup most commonly presenting for clinical evaluation and are frequently subject to adverse complications. Therefore, we have taken this opportunity to assemble longitudinal cohort data in 1,000 adult patients presenting in this midlife age group to determine the extent to which therapeutic interventions have altered clinical course.

METHODS

PATIENT SELECTION. Databases from 2 HCM centers, Minneapolis Heart Institute and Tufts Medical Center, identified 1,001 consecutive HCM patients presenting to those institutions at 30 to 59 years of age between 1992 and 2011, inclusive. Patients were referred and enrolled for targeted subspecialty evaluation, risk stratification and treatment, or to establish the diagnosis of HCM.

Recent vital clinical status up to December 2013 was obtained by hospital visit or systematic telephone contact (or by social security death index) in 1,000 patients (19). One patient was lost to follow-up due to residence outside of the United States. Complete and detailed clinical records at follow-up could be obtained in 979 of 1,000 patients (98%).

Follow-up duration from study entry (at first visit) to most recent contact or death was 7.2 ± 5.2 years (ranging to 37 years). Diagnosis of HCM was on the basis of echocardiographic and/or cardiovascular magnetic resonance (CMR) demonstration of a hypertrophied and nondilated left ventricle (LV) with wall thickness ≥13 mm, in the absence of other cardiac or systemic diseases capable of producing a similar magnitude of hypertrophy (1,2,5,6,21). Deaths due to heart failure or SD were defined as previously reported (9). Patients with known HCM phenocopies (e.g., Fabry disease, lysosomal associated membrane protein-2 (LAMP2) cardiomyopathy, or amyloidosis) were excluded. This study was reviewed and approved by Institutional Review Boards of the participating institutions Allina Health System and Tufts Medical Center, permitting use of patient medical information for research. All authors had full access to data and take responsibility for the integrity of the data and agreed to the paper as written.

IMAGING. Transthoracic echocardiographic studies were performed in standard fashion. LV wall thickness was the maximal end-diastolic dimension within the chamber (usually the ventricular septum). Continuous-wave Doppler was used to estimate the peak instantaneous LV outflow gradient. Obstruction was defined as a gradient ≥30 mm Hg, and the nonobstructive state as <30 mm Hg at rest and with exercise (20,22,23).

CMR studies were performed in 465 patients with a 1.5-T clinical scanner. Cine sequences were performed in standard views with full LV coverage. Late gadolinium enhancement (LGE) images were acquired 10 to 15 min after intravenous administration of 0.2 mmol/kg gadolinium-diethylene triamine pentaacetic acid, using a breath-held segmented inversion-recovery sequence. LGE quantification was performed by manually adjusting the gray scale threshold to visually define LGEs, which were summed and expressed as a proportion of the total LV myocardium (24).

DEFIBRILLATORS. Single- or dual-chamber ICDs capable of antitachycardia and antibradycardia pacing were implanted in 389 patients for primary (n = 383) or secondary (n = 6) prevention, according to the risk stratification model advanced for HCM in guidelines and consensus panels (1-6). Major conventional risk factors (1-3,5-8) are: 1) family history of SD due to HCM; 2) unexplained recent syncope; 3) multiple repetitive nonsustained ventricular tachycardia on ambulatory electrocardiography (ECG) monitoring; 4) hypotensive or blunted blood pressure response to exercise; 5) massive LV hypertrophy (wall thickness ≥30 mm).

Expert electrophysiologists at each center analyzed stored intracardiac electrocardiograms for arrhythmias responsible for defibrillator discharges (shocks or antitachycardia pacing), according to prior definitions

TABLE 1 Demographics, Clinical Features, and Outcome in 1,000 HCM Patients Presenting at 30 to 59 Years of Age

Age at study entry, yrs	45.7 ± 8.5
30–39	290 (29)
40–49	361 (36)
50–59	349 (35)
Age at last evaluation, contact, or death, yrs	53.2 ± 9.2 (32–80)
30–39	90 (9)
40–49	297 (30)
50–59	369 (37)
60–69	211 (21)
70–79	33 (3)
Males	704 (70)
Age at diagnosis, yrs	40.4 ± 11.3 (0.1–59)
Family history of HCM	361
Family history of HCM death	238
LVOT gradient, ≥30 mm Hg at rest	272 (27)
LVOT gradient, <30 mm Hg at rest/ ≥30 mm Hg with exercise	206
Mitral valve systolic anterior motion	655
Left atrial dimension, mm	42.3 ± 7.2 mm (20–79)
LVED transverse dimension, mm	43.9 ± 6.8 (21–97)
Maximal LV thickness, mm	21.7 ± 5.5 (13–48)
Atrial fibrillation	265 (27)
Myectomies	226*
Post-operative myectomy deaths	2 (0.8)
Alcohol septal ablations	27
Heart transplantations	25
ICDs	389†
LV apical aneurysms/ regional scarring	32
All 5 major conventional risk markers	687 (69)‡
Conventional risk factors	
0	381
1	365
2	189
≥3	65
Coronary artery disease	71§
NYHA-FC initial evaluation (1,000 patients)	
1	526 (52)
2	275 (28)
3–4	199 (20)
NYHA-FC last evaluation (patients)	
1	624 (64)
2	263 (27)
3–4	92 (9)
Drug therapy at study entry	
Beta-blockers	564
Calcium antagonists	272
Diuretic agents	113
Disopyramide	30
ACE/ARB	105
Warfarin	71
Amiodarone	18
Others (sotalol, flecainide, digitalis)	18
Contrast CMR	
Patients studied	465
Patients with LGE	200
Patients with LGE ≥15% of LV	23
% of LGE (n = 200)	6.1 ± 7.7
% of LGE in survivors (n = 175)	5.6 ± 7.4‖
% of LGE (SD/ICD terminated) (n = 12)	6.6 ± 6.9
% of LGE (severe heart failure/ death/transplant) (n = 9)	8.7 ± 9.4
Nonfatal embolic stroke	22 (2.2)
Fatal embolic stroke	2 (0.2)
Sarcomere mutations	
Myosin-binding protein C	40
β-myosin heavy chain	23
Troponin T	6
Troponin I	1
Troponin C	1
α-tropomyosin	3
Myosin-binding protein C and β-myosin heavy chain	1
Myosin-binding protein C and troponin I	2

Values are mean ± SD, n (%), mean ± SD (interquartile range), or n. *Does not include 5 patients who also underwent alcohol septal ablation; of 258 septal reduction procedures, 217 were performed after the first visit and study entry. †Includes 82 patients who received ICDs before the first visit to the participating center; of the 383 patients who received implants for primary prevention, 341 had ≥1 conventional risk marker, and among the other 42, indications were end-stage heart failure (n = 19), LV apical aneurysm (n = 12), extensive LGE (n = 3), or complete heart block after alcohol septal ablation (n = 8). ‡Hypotensive/ attenuated blood pressure response to exercise was not tested in 279 patients, but ancillary risk markers were identified in 48 other patients: LV apical aneurysm, end-stage progression, or extensive LGE. §Includes 53 patients requiring intervention (stents, bypass surgery, or percutaneous coronary procedure); 488 patients were imaged with coronary arteriography or CT angiography. ‖LGE in survivors vs. SD/ICD terminated, or vs. severe heart failure or death or transplant; p values 0.21 to 0.65.

ACE/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; BP = blood pressure; C = chronic; CMR = cardiovascular magnetic resonance; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVED = left ventricular end-diastolic dimension; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; NSVT = nonsustained ventricular tachycardia; NYHA-FC = New York Heart Association functional class; P = paroxysmal; SD = sudden death.

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in HCM studies (12). Device defibrillator discharges were considered appropriate when triggered by ventricular fibrillation or rapid sustained ventricular tachycardia (rate: >180/min). Rate cutoffs for arrhythmia detection were programmed and antitachycardia pacing activated at the electrophysiologist's discretion.

Other major interventions included septal reduction therapy (226 underwent septal myectomy; 27 had alcohol septal ablation), and 25 others underwent heart transplantation. All major HCM-related events, including out-of-hospital cardiac arrest, occurred after the initial visit to a participating institution.

STATISTICAL ANALYSES. Descriptive statistics. Data are mean ± SD for continuous variables and proportions for categorical variables; where continuous variables had skewed distributions, data are expressed as median (25th, 75th percentiles). Student *t*-test or Wilcoxon rank-sum tests assessed the

TABLE 2 Patients With HCM-Related Deaths or Major Events and Interventions

Patient #	Age at Initial Evaluation (yrs)	Sex	Age at Death or Event (yrs)	NYHA		LVOTG (at Rest) (mm Hg)	Max LV Thickness (mm)	AF	LA (mm)	% of EF	Comments
				Initial	Last						
HCM-related deaths											
Sudden cardiac death											
1	31.1	M	37.9	1	3	58	31	0	50	75	Declined ICD; NSVT; LV ≥30 mm
2	32.6	M	36.4	1	1	0	30	0	33	80	Declined ICD; syncope; LVH ≥30 mm
3	33.4	M	41.6	1	1	25	37	0	43	70	Declined ICD; family history of SD; NSVT; LV ≥30 mm
4	33.8	M	36.2	2	1	17	32	0	43	65	Pre-ICD era; LV ≥30 mm; myectomy 17 yrs prior
5	34.2	M	41.8	2	2	0	20	0	42	70	Pre-ICD era without risk factors
6	34.3	M	41.0	2	2	0	18	0	36	65	ICD failed
7	38.1	F	39.7	1	1	0	18	0	50	65	LV apical aneurysm
8	43.1	M	44.0	1	1	35	24	0	44	60	Pre-ICD era without risk factors
9	43.8	M	45.0	2	2	75	20	0	46	65	Without risk factors
10	45.6	M	52.4	2	2	0	19	C	76	60	Declined ICD; family history of SD; myectomy 15 yrs prior
11	46.0	F	50.6	1	2	30	25	0	42	65	Pre-ICD era; family history of SD; syncope; LV ≥30 mm
12	46.8	M	47.5	1	1	0	22	0	48	70	Pre-ICD era; NSVT
13	49.6	M	55.3	2	2	0	20	P	49	60	Without risk factors
14	52.9	M	58.3	2	2	0	15	0	38	65	Declined ICD; syncope; NSVT
15	53.8	M	55.6	1	1	35	17	0	48	65	Pre-ICD era without risk factors
16	56.8	M	59.1	1	1	0	19	0	41	65	Declined ICD; family history of SD; NSVT
17	58.6	M	61.4	2	2	0	23	0	46	80	Without risk factors
Advanced (end-stage) heart failure without transplant											
1	32.9	M	42.1	2	3	0	20	0	54	15	HF death 12 y post-operative myectomy
2	38.4	M	52.6	1	3	0	18	0	33	25	Declined transplant
3	39.0	M	44.6	2	3	0	17	0	52	65	Died awaiting transplant
4	39.1	M	45.5	3	3	0	18	0	33	20	Denied transplant (comorbidities)
5	39.2	M	42.0	3	3	0	22	C	79	23	Died of HF awaiting transplant; myectomy 21 yrs prior
6	42.5	F	47.9	1	3	0	17	P	33	40	Died of HF awaiting transplant; family history of end-stage HF
7	45.5	F	68.9	3	3	0	20	C	68	35	HF death 17 yrs post successful myectomy; family history of end-stage HF
8	47.8	M	67.8	2	3	0	20	0	43	60	Declined transplant; family history of end-stage HF
9	54.4	F	57.5	3	3	0	30	0	50	60	Denied transplant due to comorbidities; died 14 yrs post-myectomy
10	56.1	F	70.1	1	3	0	19	0	49	49	Declined transplant
11	57.7	F	66.1	1	3	0	28	C	55	40	Denied transplant (comorbidities)
Advanced (end-stage) heart failure without transplant and prior ICD intervention											
1	56.6	F	59.9	3	4	110	23	P	54	65	Died of HF awaiting transplant; 4 y post-myectomy; ICD shock 20 months prior to death
Post-operative											
1	44.0	M	44.3	3	3	100	25	C	48	30	Aneurysm resection and myectomy
2	44.3	M	45.6	2	3	81	17	0	46	70	Myectomy complicated by VSD
3	48.5	F	48.5	4	4	100	30	0	40	70	Myectomy and MVR
4	51.8	F	58.0	3	4	115	25	C	43	60	MVR and CABG; ASA 6.2 yrs prior
Embolic stroke											
1	36.2	M	42.1	2	2	135	19	P	43	70	In AF on warfarin; myectomy 3.7 yrs prior
2	52.8	M	61.1	2	2	36	40	P	48	65	History of AF; noncompliant with warfarin
Post-transplant deaths											
1	41.7	M	47.1	4	2	0	12	C	60	10	Died of lymphoma 18 yrs post-transplant; family history end-stage HF
2	43.7	M	46.9	3	3	0	20	0	36	45	2 heart transplants 12 yrs apart; also kidney transplant; died 2 yrs after last transplant
3	46.8	M	49.7	2	3	0	30	P	60	25	Died of Hodgkin's disease 10 yrs post-transplant
4	52.1	F	57.8	1	4	0	11	0	35	50	Died RV failure 3 days post-operative; myectomy 32.6 yrs prior
Transplant complication and prior ICD intervention											
1	45.2	F	46.4	2	2	0	14	P	60	30	ICD intervention 1.5 yrs prior to transplant; died 6 yrs post-transplant after cardiac arrest; family history of end-stage HF

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TABLE 2 Continued

Patient #	Age at Initial Evaluation (yrs)	Sex	Age at Death or Event (yrs)	NYHA Initial	NYHA Last	LVOTG (at Rest) (mm Hg)	Max LV Thickness (mm)	AF	LA (mm)	% of EF	Comments
Nonfatal HCM-related major events											
Resuscitated cardiac arrest											
1	30.7	M	37.4	1	1	0	25	P	39	70	Without risk factors
2	37.0	M	37.8	2	2	23	23	0	49	65	Family history of SD
3	50.6	M	53.0	1	1	0	17	P	37	70	Declined ICD; history of NSVT
Resuscitated cardiac arrest and ICD intervention after											
1	35.3	F	37.8	1	1	31	20	0	36	65	NSVT; ICD shock 6 months after
2	43.0	M	57.9	2	2	65	20	0	43	60	History of NSVT; CAD involving the RCA and first diagonal; currently in end-stage HF
Appropriate ICD interventions											
1	32.3	M	42.8	2	3	0	31	0	45	70	NSVT; LV ≥30 mm
2	32.6	M	37.8	1	1	0	18	0	38	65	LV apical aneurysm
3	33.0	M	36.0	2	1	75	44	0	44	70	Family history of SD; syncope; LV ≥30 mm
4	33.3	F	35.0	1	1	80	25	0	43	65	Family history of SD; abnormal BP response
5	33.7	F	39.0	1	1	0	16	0	28	65	Syncope; abnormal BP response
6	35.4	M	41.4	1	1	0	31	0	36	65	Family history of SD; syncope; NSVT; LV ≥30 mm
7	36.8	F	39.4	3	3	0	22	P	38	75	Family history of SD; abnormal BP response
8	36.9	M	37.4	1	1	65	21	P	42	60	Family history of SD
9	37.0	F	44.1	1	1	0	17	P	33	50	NSVT
10	38.1	M	65.3	1	2	0	31	P	49	60	NSVT; LV ≥30 mm
11	40.0	F	41.8	2	2	90	29	P	68	55	NSVT
12	41.4	F	42.8	1	1	0	22	0	52	55	Family history of SD; NSVT
13	42.2	M	43.4	1	1	0	23	0	30	60	NSVT
14	42.8	M	48.8	2	1	0	35	P	56	70	Syncope; LV ≥30 mm; abnormal BP response
15	42.8	M	62.9	3	2	40	25	C	48	60	Syncope; NSVT
16	44.3	F	52.3	1	1	0	25	0	35	65	Family history of SD
17	44.3	M	48.9	1	1	30	28	0	27	52	Syncope; NSVT; LV apical aneurysm
18	44.5	F	47.1	2	2	0	28	0	24	73	NSVT; LV ≥30 mm
19	44.6	F	48.6	3	3	0	15	C	53	55	End-stage HF; myectomy 12 yrs prior; declined transplant
20	44.9	F	46.2	1	1	20	21	0	38	70	Family history of SD; syncope
21	47.0	M	56.2	2	2	160	23	C	45	70	NSVT
22	48.5	F	49.9	1	1	74	18	0	50	70	Family history of SD; NSVT
23	48.6	F	49.0	3	2	0	18	0	47	60	Family history of SD; syncope
24	51.5	M	56.8	3	2	74	15	C	52	65	Family history of SD
25	51.7	M	61.6	1	1	0	28	0	42	60	Syncope; NSVT
26	53.6	M	58.3	1	1	0	30	0	36	55	LV ≥30 mm
27	53.8	F	62.1	3	3	0	21	0	45	60	Family history of SD; NSVT; LV apical aneurysm; ASA 11 yrs prior to ICD intervention; now listed for transplant
28	55.1	F	59.4	3	3	0	23	P	45	70	Family history of SD; syncope
29	57.4	M	63.4	1	1	0	19	P	40	60	Without risk factors
30	58.6	F	65.8	3	3	0	18	P	32	65	Family history of SD; syncope
31	59.6	M	68.7	3	2	65	40	P	52	80	Syncope; LV ≥30 mm
ICD interventions-appropriate and heart transplantation thereafter											
1	34.5	M	39.3	1	1	0	17	P	50	55	Syncope; NSVT; transplant 12 months after ICD intervention
2	40.6	F	43.3	3	1	0	17	P	45	50	Family history of SD; NSVT; transplant 14 months after ICD intervention

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statistical significance of continuous variables, and chi-square or Fisher exact test analyzed categorical variables.

Clinical parameters were tested as univariate predictors of HCM-related mortality or life-threatening events (n = 96). A p value of <0.05 was considered significant and was presented as 2-sided where appropriate. Variables with a p value of <0.05 for univariate associations were entered into a stepwise multivariate Cox proportional hazards model to identify independent predictors. Proportional hazards assumptions were tested graphically before proceeding. Statistical calculations were carried out using Stata version 11.2 software (StataCorp; College Station, Texas).

Survival and event analysis. For patients with known survival and event status, the fraction at each

TABLE 2 Continued

Patient #	Age at Initial Evaluation (yrs)	Sex	Age at Death or Event (yrs)	NYHA		LVOTG (at Rest) (mm Hg)	Max LV Thickness (mm)	AF	LA (mm)	% of EF	Comments
				Initial	Last						
Heart transplantation											
1	30.5	F	32.1	3	1	0	15	P	48	30	
2	32.1	M	39.2	3	1	0	30	C	55	40	Successful myectomy 7 yrs prior
3	32.5	M	50.4	1	1	0	33	0	51	69	18 yrs prior to transplant LVOTG 86 mm Hg
4	34.0	F	41.2	2	2	0	25	C	54	57	Family history of end-stage HF
5	36.7	F	45.1	3	1	0	15	0	40	45	Family history of end-stage HF
6	37.3	M	38.8	4	1	0	28	P	60	50	Successful myectomy 23 yrs prior; LVAD prior to transplant
7	39.4	M	45.9	1	1	0	15	0	46	34	
8	40.1	F	44.8	3	1	0	10	C	47	40	Family history of end-stage HF; LV remodeling
9	41.2	F	41.7	3	1	0	16	P	52	50	
10	41.4	M	47.6	3	1	0	18	C	46	15	LVAD prior to transplant
11	44.9	F	55.2	3	1	0	19	0	44	60	
12	46.3	F	49.6	2	1	0	18	P	54	30	Family history of end-stage HF
13	48.0	M	48.9	3	1	0	17	P	53	55	
14	49.4	F	58.0	1	1	0	16	P	47	55	
15	53.2	M	55.9	2	1	0	22	P	55	50	
16	54.0	M	65.7	1	1	0	16	P	55	55	LVAD prior to transplant
17	59.4	M	62.5	3	1	36	21	P	44	45	ASA 3 yrs prior; stent to LAD
18	59.6	F	61.5	3	1	0	12	C	62	49	LV remodeling

AF = atrial fibrillation; ASA = alcohol septal ablation; BP = blood pressure; C = chronic (AF); CABG = coronary artery bypass graft; CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LAD = left anterior descending; LV = left ventricular; LVAD = left ventricular assist device; LVH = left ventricular hypertrophy; LVOTG = left ventricular outflow tract gradient; MVR = mitral valve replacement; NSVT = nonsustained ventricular tachycardia on 24-hour ambulatory (Holter) electrocardiography; P = paroxysmal (AF); RCA = right coronary artery; SD = sudden death; VSD = ventricular septal defect; other abbreviations as in Table 1.

follow-up interval was estimated by the Kaplan-Meier method. The expected fraction surviving at each time after the initial visit was computed by assigning a probability of survival appropriate to age and sex, on the basis of the U.S. general population (25). Actual and expected survival fractions were compared using 1-sample log-rank tests, which also provided an estimate for the standardized mortality ratio (SMR) and 95% confidence interval (CI) (26). Computations were carried out using R version 2.36-14 software (Development Core Team 2012, R Project).

RESULTS

PATIENT DEMOGRAPHICS AND SYMPTOMS. Patients were 45 ± 8 years of age at study entry, 53 ± 9 years at the most recent evaluation (or death), and 40 ± 11 years of age at HCM diagnosis. Duration of follow-up was 7.2 ± 5.2 years. Maximal LV wall thickness was 22 ± 5 mm; ≥30 mm in 104 (10%) (Tables 1 and 2). At the initial evaluation, most patients (801 [80%]) were asymptomatic or mildly symptomatic and demonstrated New York Heart Association (NYHA) functional classes I and II. At the last evaluation, 91% were in NYHA functional classes I and II (Table 1).

MORTALITY. Of the 1,000 study patients, 918 (92%) survived over the follow-up period; 82 (8%) died (Figures 1 and 2, Table 2).

HCM-related events. In 40 patients (4% [0.53%/year]), the cause of death was attributable to HCM at 50 ± 9 years of age (range 36 to 70 years of age) (Central Illustration). Seventeen deaths were related directly to advanced heart failure in the absence of LV outflow obstruction (ejection fraction: <50% in 13 patients). These patients had conditions that were refractory to vigorous pharmacologic treatment strategies, including angiotensin-converting enzyme inhibitors (n =17), diuretic agents (n = 17), beta-blockers (n = 16), and verapamil (n = 5). Twelve of the 17 patients who died had either declined heart transplantation, were ineligible, or were waitlisted; 5 others died of transplantation-related complications (with 4 of these surviving 6 to 18 years). Two patients died of embolic stroke (0.2%) and 4 after HCM-related surgery, for example, myectomy in 3 and apical aneurysm resection in 1 (27) (Table 2).

Seventeen patients died suddenly of HCM (Figure 2, Table 2). Six of these deaths occurred 5 ± 2 years after they had declined a formal recommendation for prophylactic ICD therapy, at 47 ± 8 years of age (1-7,12). Eleven additional patients did not receive ICDs, either because they were judged to be at low risk without markers (7,28,29) or died in the 1990s, prior to systematic use of ICDs for HCM (15). None of the 40 HCM patients who died had obstructive coronary artery disease on the basis of

angiography, angina, myocardial infarction, or acute coronary event.

Non-HCM events. Forty-two patients (4.2%) died of causes unrelated to HCM (0.56%/year), including 18 of noncardiac diseases, most commonly cancer (n = 9) at 57 ± 10.1 years. In 11 of these patients, demise was due to multiple, largely noncardiac organ system abnormalities and comorbidities unlikely to be linked to HCM.

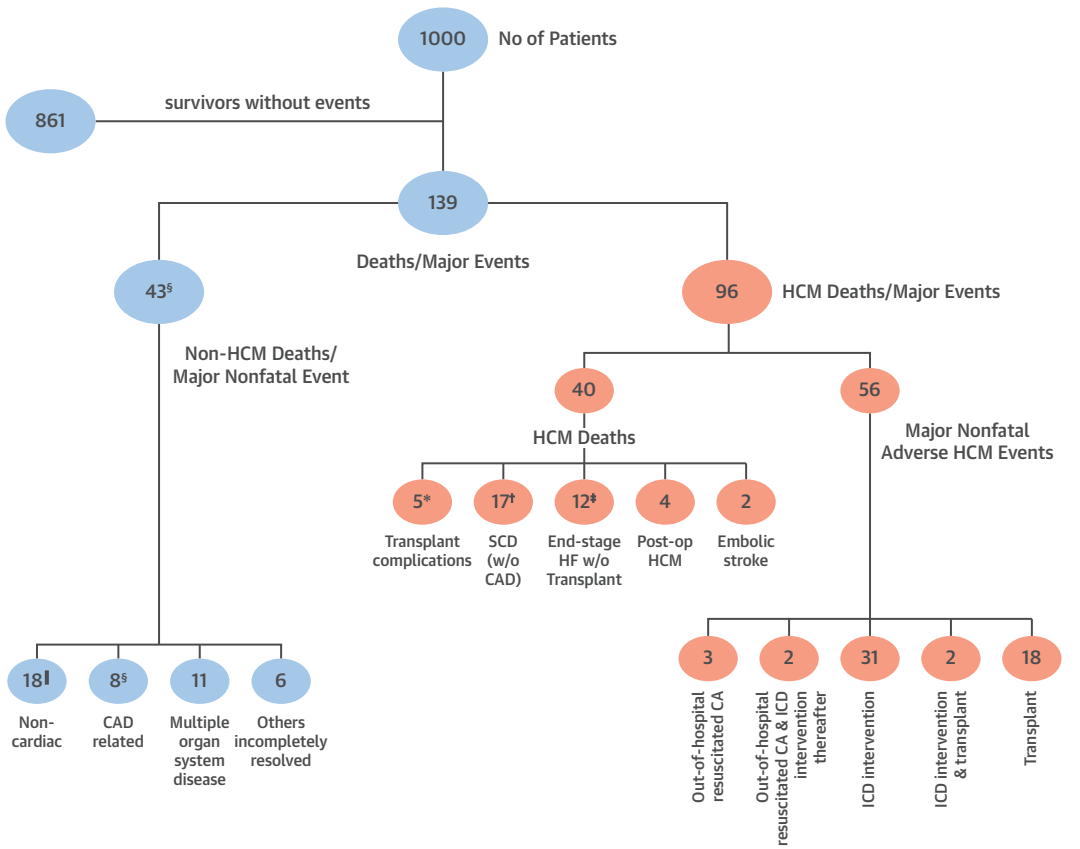
Major nonfatal HCM-related events. Fifty-six patients (5.6%) had nonfatal HCM-related events at 0.79%/year (Figure 1, Table 2).

ICD interventions. Of the 389 patients with ICDs, 37 experienced ≥1 appropriate ICD intervention for ventricular tachycardia (VT)/ventricular fibrillation (VF); (5-year cumulative probability: 8.1%), including 13 patients with ≥2 defibrillation shocks (Central Illustration). The first ICD intervention was at 50 ± 10 years (range 35 to 38 years), with median interval for implantation to the first appropriate intervention of 2.7 years (ranging up to 13.5 years).

Of these 37 patients, 14 had 1 risk factor and 23 had 2 or 3 risk factors, including nonsustained VT on ambulatory (Holter) ECG (n = 19); family history of HCM-related SD (n = 16); unexplained syncope (n = 14); massive LV hypertrophy ≥30 mm (n = 8).

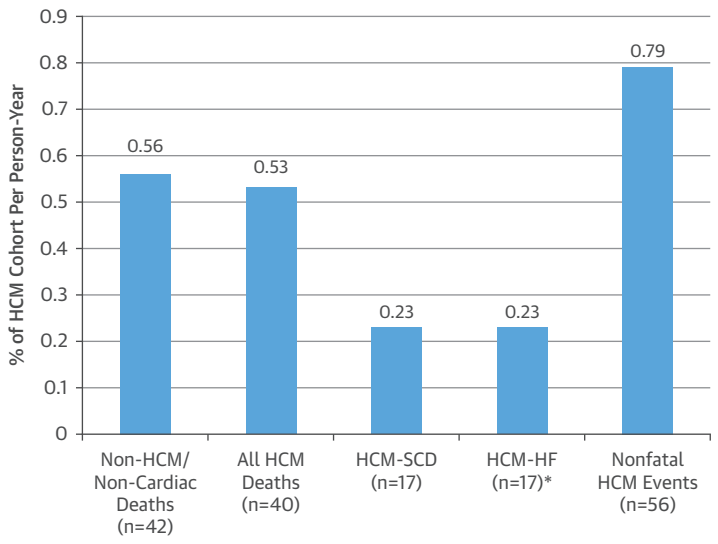
One or more inappropriate ICD shocks occurred in 47 patients (12%; 5-year cumulative probability of 11.1%), including 4 with appropriate interventions. Thirty-five patients (95%) are currently alive 4.8 ± 3.9 years after the first ICD intervention (up to 18 years) at 53 ± 8 years of age.

FIGURE 1 Natural History of HCM in Midlife Adults



Summary of clinical outcomes in 1,000 individual HCM patients, 30 to 59 years of age, at study entry. *Appropriate ICD shocks 1.5 years prior to transplant and 6.1 years before death from transplantation complications. †1 patient died despite ICD in place. ‡1 patient with an appropriate ICD shock 20 months prior to death from heart failure. §Includes 1 survivor with CAD, resuscitated cardiac arrest, and myocardial infarction. ‖Includes 1 patient with resuscitated out-of-hospital cardiac arrest unrelated to HCM 4 years before death. AF = atrial fibrillation; CA = cardiac arrest; CAD = coronary artery disease; CV = cardiovascular; ICD = implantable cardioverter-defibrillator; HCM = hypertrophic cardiomyopathy; HF = heart failure; SCD = sudden cardiac death; VT/VF = ventricular tachycardia/ventricular fibrillation; w/o = without.

FIGURE 2 HCM Mortality Rates in Midlife Adults



Mortality rates per person-year in 1,000 HCM patients initially evaluated at 30 to 59 years of age. *Includes 5 transplant-related deaths. SCD = sudden cardiac death; other abbreviations are as shown in Figure 1.

Five additional patients were resuscitated after out-of-hospital cardiac arrest, aided by timely therapeutic hypothermia in 3 cases (30). All survived to the end of follow-up at 5.1 ± 3.3 years, 2 with a secondary prevention ICD shock.

Advanced heart failure and transplant. Twenty of 25 patients (80%) with nonobstructive HCM undergoing heart transplantation (at 48 ± 7 years) for unrelenting drug-refractory heart failure symptoms (ejection fraction: <50% in 17) have survived 4 ± 4 years (to 17) postoperatively, at 51 ± 9 years (Central Illustration).

Of the 258 patients who underwent surgical septal myectomy (31), alcohol ablation (32), or both, to relieve obstruction and severe heart failure symptoms, 232 (90%) are alive at age 53 ± 8 years, of whom 207 are improved in NYHA functional classes I and II. Myectomy or alcohol ablation patients progressed to heart transplantation at a rate similar to that in other patients (4.4%/year vs. 4.7%/year; log-rank p = 0.61).

Eleven other patients were potential candidates for septal reduction with large outflow gradients (>50 mm Hg) and NYHA functional classes III and IV symptoms, but 8 refused this therapy and 3 were ineligible due to comorbidities. Over a follow-up period of 5.8 ± 3 years, 9 of these patients survived.

EVENT RATES. Aborted HCM mortality, that is, nonfatal sudden events/interventions, including appropriate ICD interventions, heart transplantation, and resuscitated out-of-hospital cardiac arrest occurred in 56 patients, 0.79%/year, which is 50% higher than the HCM mortality rate (Figures 1 and 2). Multivariate independent predictors of HCM mortality and life-threatening events (n = 96) were younger at diagnosis, had increased left atrial dimension, and female sex (Table 3).

The HCM-related morality rate was 0.53%/year (Central Illustration). Considering only HCM-related deaths, survival rates at 5 and 10 years were 98% (95% CI: 96% to 98%) and 94% (95% CI: 91% to 95%), respectively, and notably, no different than that expected for all-cause mortality in an age- and sex-matched general U.S. population (SMR: 0.83; 95% CI: 0.61 to 1.14; log-rank p = 0.25) (Figure 3B). The combination of HCM-related deaths and life-threatening events aborted by contemporary treatments significantly exceeded all-cause mortality in the general population (SMR: 2.11; 95% CI: 1.73 to 2.58; log-rank p < 0.001) (Figure 3C).

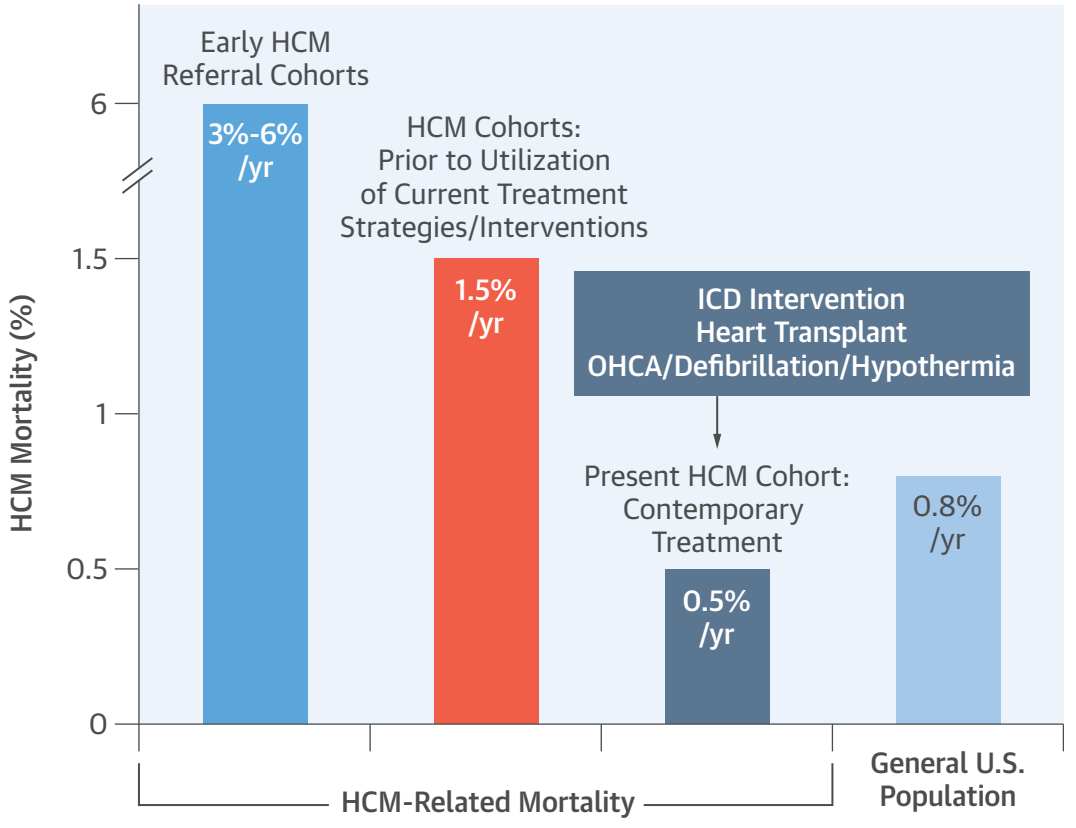
All-cause mortality in HCM patients (n = 82; 8.2%) was 1.16%/year, exceeding that expected in a general age and sex-matched U.S. population (SMR: 1.68; 95% CI: 1.35 to 2.08; log-rank p < 0.001) (Figure 3A). Survival rates at 5 and 10 years were 97% (95% CI: 95% to 97%) and 88% (95% CI: 84% to 90%), respectively.

DISCUSSION

Over the last 15 years, comprehensive HCM-related management strategies have evolved considerably, including an expanded risk stratification algorithm with greater appreciation for at-risk patients, leading to more reliable identification of those likely to achieve SD prevention with ICDs (10–16) and in accordance with U.S. guidelines (5,6), HCM patients have also benefited from relief of heart failure symptoms and extended longevity due to advances in surgical septal myectomy technique (or alcohol ablation) and heart transplantation (1–6,10–18,31,32). Although the effectiveness of such treatments has been reported in selected high-risk subsets (12–15), ascertaining their true efficacy on clinical course, potential mortality, and longevity requires systematic assessment in established and consecutively assembled large adult HCM patient populations (such as the present one).

We recently recognized patient age as important in the natural history and clinical course of HCM, and decisions governing major treatment interventions (19,33), by demonstrating that advanced age (≥60 years) is associated with a low disease event rate (19). Thus, in the present study, we longitudinally tracked the impact of major treatment initiatives on

CENTRAL ILLUSTRATION **Decreasing Mortality Due to HCM**



Maron, B.J. et al. J Am Coll Cardiol. 2015; 65(18):1915–28.

Historical 50-year reduction in HCM-related mortality to the current rate of 0.5%/year, achieved with contemporary management strategies, and in comparison to the age- and sex-matched general population. HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; OHCA = out-of-hospital cardiac arrest.

the clinical course of adult patients between 30 and 59 years of age, with the rationale that the "midlife" age group is most often encountered for diagnosis or evaluation in clinical practice, as well as at-risk for adverse disease-related events, including SD and heart failure progression (1-3,5,9,12,15,16,31). We elected not to incorporate younger HCM patients in this report, who are encountered much less frequently in practice, and often with early onset aggressive disease expression (1-3,5,6,33-35).

Using our investigative strategy, we believe that the expectation for longevity is favorably altered for many HCM patients presenting in midlife, with a low mortality rate directly attributable to utilization of contemporary cardiovascular treatment options (**Central Illustration**). It was not possible, however, to assemble an untreated and rigidly matched control group to address the improved HCM mortality reported here. Nevertheless, it is a reasonable assertion that, in a cohort analysis such as ours, it is highly unlikely that patients would have survived to the present without treatment interventions known to preserve life, such as ICDs, surgical myectomy, heart transplantation, modern external defibrillation techniques (and therapeutic hypothermia), or prevention of embolic stroke death with prophylactic anticoagulant drugs.

For example, the HCM mortality rate among our 1,000 patients was just 0.5%/year, approximately 10-fold lower than the 3% to 6%/year reported from tertiary referral cohorts in a much earlier era, influenced by highly skewed patient referral patterns (34-39). Our HCM mortality rate documented here was also 3-fold less than the 1.5% annual HCM-related rate of death attached to this disease in the pre-ICD era (39).

TABLE 3 Univariate and Multivariate Predictors of HCM-Related Mortality or Life-Threatening Event

	Univariate				Multivariate	
Parameter	HCM Death or Event (n = 96)	No HCM Death or Event (n = 904)	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age at diagnosis, yrs	34.8 ± 12.2	41.0 ± 11.0	0.963 (0.947–0.980)	<0.001	0.967 (0.951–0.983)	<0.001
Age of first evaluation, yrs	43.8 ± 8.2	45.9 ± 8.5	0.986 (0.962–1.009)	0.24		
Males	58 (60.4)	645 (71.4)	0.587 (0.389–0.886)	0.011	0.611 (0.400–0.933)	0.023
LVOT gradient ≥30 mm Hg at rest	27 (28.1)	245 (27.1)	1.084 (0.694–1.693)	0.72		
Left atrial dimension, mm	46.0 ± 9.8	41.9 ± 6.7	1.064 (1.040–1.090)	<0.001	1.048 (1.048–1.024)	<0.001
LVED transverse dimension, mm	45.2 ± 6.7	43.7 ± 6.8	1.025 (0.993–1.058)	0.13		
Maximal LV thickness, mm	23.1 ± 6.8	21.6 ± 5.3	1.033 (0.999–1.067)	0.057		
Atrial fibrillation	46 (47.9)	219 (24.2)	1.931 (1.291–2.892)	0.001		
Presence of LGE*	21/25 (84.0)	179/440 (40.7)	5.250 (1.793–15.367)	<0.001		
NYHA functional class at study entry						
I	39 (40.6)	487 (53.9)				
II	27 (28.1)	248 (27.4)	1.544 (0.939–2.539)	<0.001		
III/IV	30 (31.3)	169 (18.7)	2.601 (1.606–4.211)			
NYHA functional class at most recent evaluation						
I	48 (20.0)	576 (65.2)				
II	24 (25.0)	239 (27.1)	1.119 (0.683–1.834)	<0.001	2.488 (1.514, 4.088)†	0.001
III/IV	24 (25.0)	68 (7.7)	3.457 (2.116–5.647)			

Values are mean ± SD or n (%). *n = 465 patients; this variable was excluded from multivariate analysis. †NYHA functional class I was used as a reference at respective time points.
Abbreviations as in Table 1.

The older mortality estimates contributed to the characterization of HCM as an untreatable disease with a uniformly grim prognosis, a view that has unfortunately persisted, in part, to the present (10,20,40).

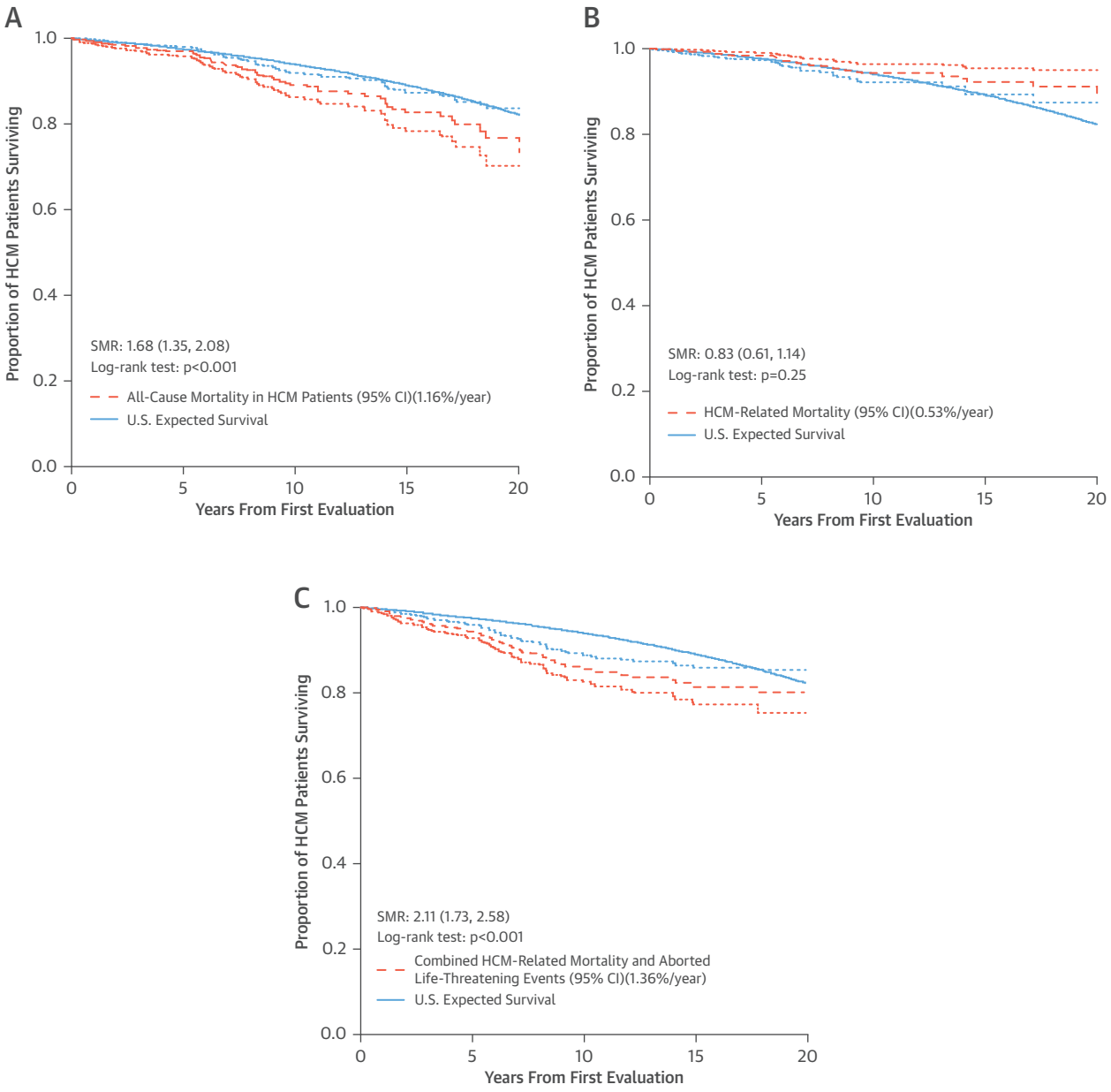
The relatively low HCM mortality rate of 0.5%/year reported here is largely attributable to aborted and nonfatal events, by virtue of utilizing the ICD for primary prevention of SD, as well as heart transplantation for prevention of heart failure-related death (**Central Illustration**). Indeed, when fatal and nonfatal HCM events were combined, the overall HCM event rate exceeded that in the general population, underscoring the survival advantage provided by major and contemporary therapeutic interventions translated to HCM here. Furthermore, our HCM mortality did not differ significantly from that expected in the general population, or that previously reported in HCM patients presenting ≥60 years of age (19). This revised perception of HCM-related mortality can serve as a measure of reassurance to many HCM patients, and evidence of what is possible in this disease with contemporary treatment.

Close inspection of clinical profiles in patients with HCM-related death showed that many of the SDs that occurred would be potentially preventable by current practice standards (1-7,10). For example, several patients declined the ICD, even after receiving a standard formal recommendation for prophylactic device therapy (1-3,5-7,12-15). Other patients were first evaluated in the 1990s, an era preceding penetration of ICDs into clinical practice for HCM and the availability of data supporting the efficacy of device therapy in this disease (15), or the expanded risk stratification models currently in use (1-3,5,6,16,27). Should these patients be hypothetically considered as likely survivors (with ICDs), the HCM-related mortality rate would decrease to 0.4%/year.

Notably, 95% of our patients with appropriate ICD interventions for VT/VF have survived to date, with the vast majority experiencing favorable quality of life with no or mild symptoms. Also, at the most recent follow-up, 80% of heart transplant patients had survived, representing a significant extension in life expectancy (17).

Our data support the evidence-based risk stratification strategy currently in widespread practice by most HCM investigators and clinicians (1-3,5-7,10-15) and in turn are supported by American College of Cardiology/American Heart Association consensus guidelines (5,6). Individual HCM patients can become ICD candidates on the basis of 1 or more major SD risk factors in their clinical profile. This strategy has proved effective in identifying most high-risk HCM patients for prophylactic ICD implantation and SD prevention (1-3,11-15), although different from that used in coronary artery disease (41,42) or the complex statistical/mathematical formula recently advanced in HCM by O'Mahony et al. (8) for the European

FIGURE 3 **Survival in Midlife HCM Adults**



Kaplan-Meier survival curves in 1,000 HCM patients, with relevant comparisons between subgroups and to expected all-cause mortality in the U.S. general population, matched for age and sex. **Dotted lines** represent 95% confidence intervals for survival probability. **(A)** All-cause mortality in HCM patients versus general population. **(B)** HCM-related mortality versus all-cause mortality in the general population. **(C)** Combined life-threatening HCM events aborted by treatment interventions and HCM-related mortality versus all-cause mortality in the general population. HCM = hypertrophic cardiomyopathy.

Society of Cardiology Guidelines (43). However, the fact that some patients in our cohort study experienced SD without conventional risk factors (1-3,6,28,29) suggests the need for additional markers in HCM, such as extensive LGE with quantitative contrast CMR (24), which creates additional candidates for ICDs and potentially results in even lower HCM-related mortality.

In this study, 37 patients prospectively identified as high-risk ultimately experienced potentially lethal

ventricular tachyarrhythmias that were terminated by the ICD, dispelling the myth that risk markers in HCM are relatively poor predictors (20,40). Nevertheless, the number of ICDs required to generate 1 implant that eventually intervened appropriately was approximately 9:1, similar to that in randomized trials of high-risk and clinically compromised patients with coronary artery disease (41,42) or nonischemic cardiomyopathy (44). However, because the arrhythmogenic substrate in HCM has proven unpredictable (1-3,10-15) and many at-risk patients are identified at young ages (5,6,12,33,45), the present cross-sectional study design does not exclude the possibility that additional appropriate ICD interventions will continue to occur in this cohort over time.

A substantial proportion of our patients died of advanced heart failure or underwent heart transplantation, suggesting that the epidemiology of HCM-related mortality may be evolving to a new paradigm in which end-stage heart failure (and its treatment) is a more major component of the disease spectrum than previously considered (16). It is even possible that progressive advanced heart failure could soon replace arrhythmic SD as the predominant cause of demise in HCM (1,2,5,6,16-18). This shift may be explained, in part, by SD prevention with ICDs or greater recognition of severe heart failure in HCM and its implications.

Over 5 decades, severe limiting drug-refractory symptoms and progressive heart failure due to LV outflow obstruction have been treated effectively by surgical septal myectomy, resulting in reversal of heart failure and greatly improved quality of life, long-term survival equivalent to the general U.S. population (31), and possible reduction in SD risk (46). Performed with low operative risk (1,2,5,6,31,46,47), 90% of patients undergoing myectomy have survived to end of follow-up (HCM-related death in <5%), with improved quality of life attributable to abolition of the outflow gradients responsible for heart failure symptoms (1,2,31). Taken together, these observations underscore the range of therapies effective in extending longevity (and improving quality of life) now available to HCM patients.

STUDY LIMITATIONS. A large, well-defined study cohort, as presented here, permits detailed assessment of the impact of major treatment interventions on the clinical course of individual HCM patients. However, assessing changes in mortality rates over time with controlled comparisons between treated and untreated patient groups in a heterogeneous and relatively uncommon disease, such as HCM is an impractical aspiration. Finally, by demonstrating in principle what can be achieved optimally in a focused HCM environment, our data (although assembled from tertiary referral centers) are relevant to more general and less highly selected HCM patient populations (48,49).

CONCLUSIONS

This large, longitudinal, midlife cohort study underscores the important principle that HCM has evolved as a contemporary disease, now with the potential to achieve a relatively low disease-related mortality rate in the range of 0.5%/year. To this purpose, we have used currently available major treatment strategies and interventions in a large subset of the HCM population (**Central Illustration**). Notably, systematic utilization of the ICD to prevent SD has altered the clinical disease course for many high-risk HCM patients. As a consequence, the epidemiology of HCM-related mortality is evolving, with advanced heart failure emerging as a more major component of the disease spectrum than previously regarded.

These data redefine the mortality risk and alter the historical perception of HCM as a relentless and progressive disease with limited effective treatment options. In the process, we provide a measure of reassurance to patients presenting in midlife, offering many a reasonable aspiration for acceptable quality of life and extended longevity.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: With appropriate management, adult patients with HCM can generally enjoy longevity comparable to age-matched and sex-matched individuals in the general population.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: Physicians should discuss with patients with HCM the array of contemporary management options available and offer reassurance (when appropriate) that with such therapy they can aspire to normal or nearly normal longevity and good quality of life.

TRANSLATIONAL OUTLOOK: Continued research is needed to identify with greater precision patients with HCM who benefit from specific therapeutic modalities, and to define the optimal timing for various interventions.

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