Impact of Effective Management Strategies on Patients With the Most Extreme Phenotypic Expression of Hypertrophic Cardiomyopathy

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Advances in treatment options for hypertrophic cardiomyopathy (HC) have proven effective in many patients for promoting favorable long-term outcomes. Whether this expectation is similar for patients with the most extreme expression of massive left ventricular (LV) hypertrophy, a particularly aggressive form of the disease is unresolved. Of 1,766 consecutive HC patients presenting to Tufts HC Institute (2004 to 2015), 92 were identified with extreme LV wall thickness (30 to 48 mm), and compared with 1,674 HC patients with less marked hypertrophy (13 to 29 mm). Follow-up assessment was over 5.3 ± 3.4 years. Patients with massive LV hypertrophy (n = 92) had higher sudden death event rates (3.0%/year) than did patients with lesser hypertrophy (0.8%/year; p <0.001). In 16 of the 92 patients (17%), potentially lethal ventricular tachyarrhythmia were successfully aborted by primary prevention implantable cardioverter defibrillator (ICD) therapy at 30 ± 13 years (n = 11), or by resuscitated cardiac arrest with external defibrillation (n = 5) and later by secondary prevention interventions (n = 3); no patient experienced arrhythmic sudden death. Aborted sudden death events (3.0%/year) exceeded HC-related mortality by 7-fold (n = 2; 0.4%/year; p <0.001). European Society of Cardiology risk score would have failed to identify 60% of patients with arrhythmic sudden death events, leaving them exposed to sudden death without ICDs. In addition, 35 patients required surgical myectomy for progressive heart failure due to LV outflow obstruction (improved to NYHA I/II in 30). Eighty-eight (96%) of the 92 patients have survived to age 38 ± 14 years (23% ≥ 50 years). All-cause mortality did not differ from an age and gender-matched general population (p = 0.62). In conclusion, in this referral-based population, patients with the most extreme expression of HC are at increased arrhythmic sudden death risk reliably prevented with prophylactic ICDs. Progressive heart failure secondary to outflow obstruction was reversible with surgical myectomy. Despite extreme phenotypic expression, with contemporary treatment interventions young HC patients have an opportunity to achieve extended survival with good quality of life. **(Am J Cardiol 2019;124:113−121)**

Hypertrophic cardiomyopathy (HC) patients with massive degree of left ventricular (LV) hypertrophy have traditionally been regarded as a subgroup with a uniformly relentless clinical course and unacceptable risk for adverse outcome, including most prominently arrhythmic sudden death and progressive heart failure.[1−8] Whether treatment interventions with implantable cardioverter defibrillators (ICDs) for sudden death prevention and surgical myectomy to reverse refractory heart failure secondary to outflow obstruction are effective in such patients, as they have proven to be for other HC subgroups, is incompletely resolved.[9−18] Indeed, there may be a hesitancy to aggressively treat young patients in this subgroup given uncertain expectations regarding outcome and/or concern for possible device-related complications. Therefore, it is timely to define the clinical course and the effectiveness of contemporary treatment on the outcome of HC patients with the most extreme phenotypic expression within the broad spectrum of this disease.

METHODS

The database of the Tufts Medical Center HC Institute was accessed from 2004 to 2015. A total of 1,766 consecutive patients had been referred to establish a HC diagnosis, or for targeted subspecialty evaluation and therapy. Among these patients, 92 (5.4%) were identified with an extreme degree of LV hypertrophy by imaging with echocardiography and/or cardiovascular magnetic resonance (CMR).[19,20] As is our practice and that of other investigators,[3] extreme LV hypertrophy was defined by an absolute LV wall thickness cut-off of ≥30 mm (independent of age and body surface area) in accord with 2003 ACC/European Society of Cardiology (ESC) and 2011 ACC/AHA guidelines for HC.[19,20] Patients with LV hypertrophy and known phenocopies of HC were excluded by clinical profile and/or

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genetic testing, for example, Fabry disease, lysosomal-associated membrane protein-2 cardiomyopathy, or amyloidosis (n = 26).[19,21]

Recent comprehensive vital clinical and survival status was obtained in each of the 92 patients with extreme LV hypertrophy by hospital visit or by telephone contact, with patients, family members, or referring physicians. Duration of follow-up was 5.3 ± 3.4 years (range to 13) from initial evaluation (study entry), and 12.4 ± 8.6 years (to 36 years; total of 1,145 patient years) from initial HC diagnosis.

Outcomes in the 92 HC patients with extreme degrees of LV wall thickness (≥30 mm) was compared with the 1,674 consecutive HC cohort with less marked degrees of hypertrophy (13 to 29 mm) evaluated during the same time interval as the primary study patients. The study population (n = 1,766) was also divided into 4 subgroups according to maximum LV wall thickness: 15 to 19 mm, 20 to 24 mm, 25 to 29 mm, and ≥30 mm, with these arbitrary cut points consistent with criteria used in previous studies.[3]

Echocardiography studies were performed in each of the 92 study patients. LV wall thickness was taken as the largest dimension measured at any site in the chamber at end-diastole. Particular care was taken to ensure that LV wall thickness measurements excluded RV (crista-supraventricularis) and LV muscle bundles, trabeculations, and papillary muscles. Peak instantaneous LV outflow tract gradient was measured at rest with continuous wave Doppler interrogation.[22] Patients with gradients <50 mm Hg at rest had symptom-limited exercise (stress) testing with echocardiography on a standard Bruce protocol as previously described.[22]

CMR studies were performed in 42 study patients using a 1.5-T clinical scanner and cine sequences in 3 long-axis planes and sequential short-axis slices from the atrioventricular ring to the apex. Late gadolinium enhancement (LGE) images were acquired using a breath-held segmented inversion-recovery sequence, and LGE quantification was performed by manually adjusting the gray scale threshold to visually define areas of LGE, which were summed and expressed as a proportion of total LV myocardium.[23]

Single- or dual-chamber ICDs capable of antitachycardia and antibradycardia pacing were implanted in 84 patients for primary (n = 79) or secondary (n = 5) sudden death prevention, with decision-making in accord with the 2003 ACC/ESC and 2011 ACC/AHA guidelines for HC.[19,20] Eight patients declined a recommendation for ICD implantation.

Massive LV hypertrophy was the sole risk factor and basis for primary prevention ICD implant in 30 patients. The other 49 massive LV hypertrophy patients also had 1 (n = 32), 2 (n = 12), or ≥3 (n = 5) additional high risk markers, most commonly family history of sudden death (n = 24), multiple repetitive and/or prolonged nonsustained ventricular tachycardia (NSVT) on ambulatory monitor (n = 22), and/or previous unexplained syncope (n = 20). In 5 patients ICDs were placed for secondary prevention after successful resuscitation from out-of-hospital cardiac arrest.

Age at ICD implant was 30 ± 13 years (range 9 to 64), with 25 patients ≤20 years. Expert electrophysiologists analyzed and adjudicated stored intracardiac electrocardiograms to characterize ventricular tachyarrhythmias responsible for defibrillator interventions.

ESC sudden death risk score was calculated using clinical variables at the time of study entry for each study patient ≥16 years of age, before septal myectomy.[21,24] The ESC risk model introduces a set of 7 binary or continuous prognostic variables into a formula. An online calculator generates a prognostic index score promoted as predictive of SD risk projected over 5 years, and with patients stratified into 3 groups for ICD recommendations: <4%/5 years (ICD generally not considered); 4% to 6%/5 years (ICD can be considered), and ≥6%/5 years (ICD should be considered). In patients with initial appropriate ICD interventions occurring >5 years after study entry, ESC risk scores were recalculated at the clinical visit just before the delayed ICD intervention. In accord with previous publications, ESC risk scores were compared with the end points of either appropriate ICD intervention, resuscitated cardiac arrest, or sudden death.[21,24]

Data are mean ± SD for continuous variables and proportions for categorical variables. Student's *t* test and ANOVA tests were used to assess the statistical significance of continuous variables, and chi-square or Fisher's exact test for categorical variables. Values of $p \leq 0.05$ were considered significant; all are reported as 2-sided. For patients with known survival and event status, the fraction at each follow-up interval was estimated by the Kaplan-Meier method. Survival analysis calculations of nonfatal sudden death events or heart failure progression excluded those patients with events that occurred before initial clinical evaluation at our center. Follow-up time for each patient was calculated from their date of initial evaluation to most recent contact or event/death. Patients who did not experience events at their most recent contact were censored in the analysis. The expected fraction surviving at each time after the initial visit was computed by assigning a probability of survival appropriate to age and gender, on the basis of the US general population. Differences in survival or clinical events between patient groups were assessed using the log-rank test. Statistical calculations were performed using SAS Enterprise Guide, version 7.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The 92 study patients were 26 ± 13 years of age at diagnosis, and 33 ± 14 years at initial evaluation, including 11 patients ≤18 years (12%), and 12 patients >50 years (21%) (Table 1). In 55 patients (60%) LV gradients were present either at rest (n = 46) or with physiologic (exercise) provocation (n = 9), and absent in the remaining 37 patients (40%).

Maximum LV wall thickness was 32 ± 3 mm (Figures 1 and 2). Extreme wall thickness ≥30 mm was confined to one LV segment in 60 patients (65%), or diffuse in 2 to 3 segments in 26 patients (28%), or ≥4 segments in 6 (7%). Also, 71 of the 92 patients (77%) had LV wall thickness of 25 to 29 mm in ≥1 additional LV segment, including 30 patients with 3 or more segments of 25 to 29 mm. Of the 42 patients with CMR studies, LGE was present in 40 (95%) occupying 9 ± 5% of LV, including 9 patients (19%) with extensive LGE ≥ 15% of LV mass.

Table 1
Demographic and clinical variables of hypertrophic cardiomyopathy patients with massive left ventricular hypertrophy as compared with 1,674 hypertrophic cardiomyopathy patients with less severe hypertrophy

	Left ventricular hypertrophy		p Value
	Massive (n = 92)	Nonmassive (n = 1,674)	
Variable			
Males	65 (71%)	1039 (62%)	0.12
Age at initial evaluation (years)	33 ± 14	52 ± 17	<0.01
Age diagnosis (years)	26 ± 13	47 ± 18	<0.01
Age most recent evaluation (years)	38 ± 14	57 ± 16	<0.01
Maximum LV thickness (mm)	32 ± 3	19 ± 4	
Maximum LV wall thickness ≥35 mm	14 (15%)	0 (0%)	
Ejection fraction, (%)	66 ± 4	63 ± 6	<0.01
Left atrial dimension (mm)	42 ± 8	41 ± 7	0.27
LV end diastolic dimmension (mm)	40 ± 6	42 ± 7	0.01
LV outflow gradient, ≥30 mm Hg at rest	46 (50%)	620 (37%)	0.01
LV outflow gradient, <30 mm Hg at rest and ≥50 mm Hg-exercise	9 (10%)	278 (17%)	0.08
Family history of HC	40 (43%)	402 (24%)	<0.01
Family history HC-related death	24 (26%)	174 (10%)	<0.01
Unexplained syncope	20 (22%)	204 (12%)	0.01
Nonsustained ventricular tachycardia on ambulatory Holter-monitor	26 (28%)	264 (16%)	<0.01
Coronary artery disease	9 (10%)	265 (16%)	0.12
Atrial fibrillation	17 (18%)	484 (29%)	0.03
Contrast-CMR			
Number with CMR studies	42	1104	
LV mass index (g/m^2)	121 ± 41	80 ± 28	<0.01
Number with late gadolinium enhancement (%)	40 (95%)	624 (57%)	<0.01
% late gadolinium enhancement	8.9 ± 5.2	5.6 ± 5.7	<0.01
Number with late gadolinium enhancement ≥15% of LV	9 (19%)	44 (7%)	0.01
NYHA-FC, initial evaluation			
I	35 (38%)	661 (39%)	0.01
II	37 (40%)	460 (27%)	
III/IV	20 (22%)	553 (33%)	
Drug therapy			
Beta-blockers	81 (88%)	1318 (79%)	0.03
Calcium channel-blockers	48 (52%)	717 (43%)	0.08
Disopyramide	5 (5%)	163 (10%)	0.17
Anticoagulants	19 (21%)	434 (26%)	0.26
Genetic testing performed	27	275	
Myosin binding protein C	9	60	
Myosin heavy chain 7	4	22	
Cardiac troponin T2	1	9	
Myosin light chain 2/3	1	1	
Number patients with ICDs	84 (91%)	418 (25%)	<0.01
Number with aborted sudden death events	16 (17%)	84 (5%)	<0.01
Appropriate ICD Interventions	14*(15%)	68† (4%)	<0.01
Resuscitated cardiac arrest	5* (5%)	25† (1%)	0.02
Septal myectomy	35 (38%)	506 (30%)	0.11
Postoperative NYHA-FC I/II	30 (86%)	477 (95%)	0.01
Postoperative NYHA-FC III/IV	5 (14%)	23 (5%)	
Alcohol septal ablation	1‡ (1%)	134 (8%)	0.02
End-stage heart failure	7§ (8%)	79¶ (5%)	0.25
Ejection fraction < 50%	3 (3%)	31 (2%)	0.34
Ejection fraction > 50%	4 (4%)	48 (3%)	0.48
Heart transplant	1 (1%)	30 (2%)	0.62
NYHA-FC, last evaluation**			
I	50 (57%)	894 (58%)	0.86
II	33 (37%)	527 (34%)	
III/IV	5 (6%)	97 (6%)	
Deaths	4 (4%)	127 (8%)	0.25
Non-HC death	2†† (2%)	102‡‡ (6%)	0.12
HC-related death	2 (2%)	25 (1%)	0.65

(*continued*)

Table 1 (*Continued*)

	Left ventricular hypertrophy		p Value
	Massive (n = 92)	Nonmassive (n = 1,674)	
Sudden death	0	5	
Heart failure death	1	9	
Post-transplant death	0	3	
Postoperative death	0	6	
Stroke death	1	2	

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

Symbols:

* Includes 3 patients with resuscitated cardiac arrest and subsequent appropriate ICD interventions.

† Includes 9 patients with resuscitated cardiac arrest and subsequent appropriate ICD interventions.

‡ Unsuccessful alcohol septal ablation performed before initial visit with subsequent septal myectomy.

§ Includes 5 patients with previous myectomy.

¶ Includes 23 patients with previous myectomy.

** In 88 surviving patients with LV wall thickness ≥30 mm, and 1,645 surviving patients with less severe left ventricular hypertrophy.

†† Probable noncardiac death but precise cause unknown in 2 patients (1 patient at age 41 with ICD and without ventricular-tachyarrhythmias; and 1 patient at age 39 with co-morbidities).

‡‡ Probable non-cardiac death but precise cause unknown in 6 patients.

Of the 92 patients, 88 (96%) survived to end of follow-up (age 38 ± 14) with 20 (23%) ≥50 years of age (range to 70), and including 42 (46%) with benign clinical course in NYHA classes I or II. Four patients (4%) died at 46 ± 10 years of age, with 2 attributable to HC (0.4%/year): embolic stroke at age 61 with atrial fibrillation (who declined anticoagulation), and advanced heart failure at age 41 during transplant evaluation. No patient experienced sudden cardiac death. All-cause (total) mortality was 0.8%/year. Survival at 5 and 10 years (considering only

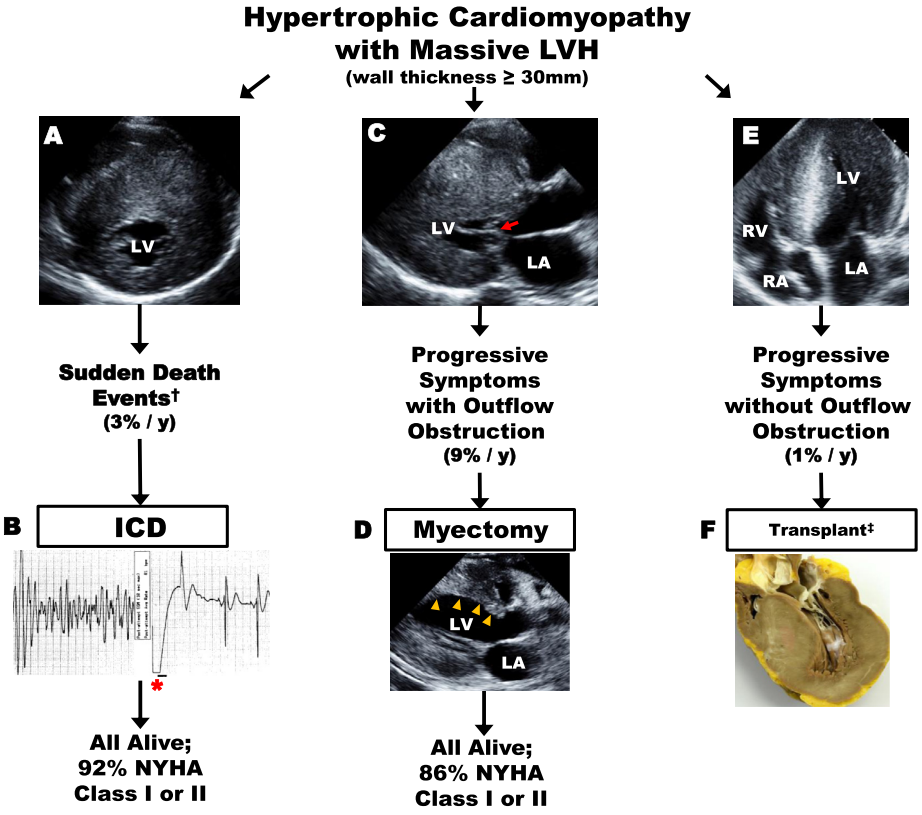

Figure 1. Impact of treatment interventions on outcome in HC patients with massive LV hypertrophy. (A and B) Risk for and prevention of sudden death with primary prevention ICDs. (C and D) LV outflow obstruction with relief of subaortic gradient and reversal of heart failure symptoms by myectomy (arrowhead). (E and F) Absence of obstruction associated with progressive end-stage heart failure leading to consideration for heart transplant.

Abbreviations: LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Symbols: * defibrillation shock terminates VF and restores sinus rhythm; † includes 6 patients also with myectomy; ‡ 1 transplant, 3 currently listed, 2 declined, and 1 died (includes 5 patients postmyectomy).

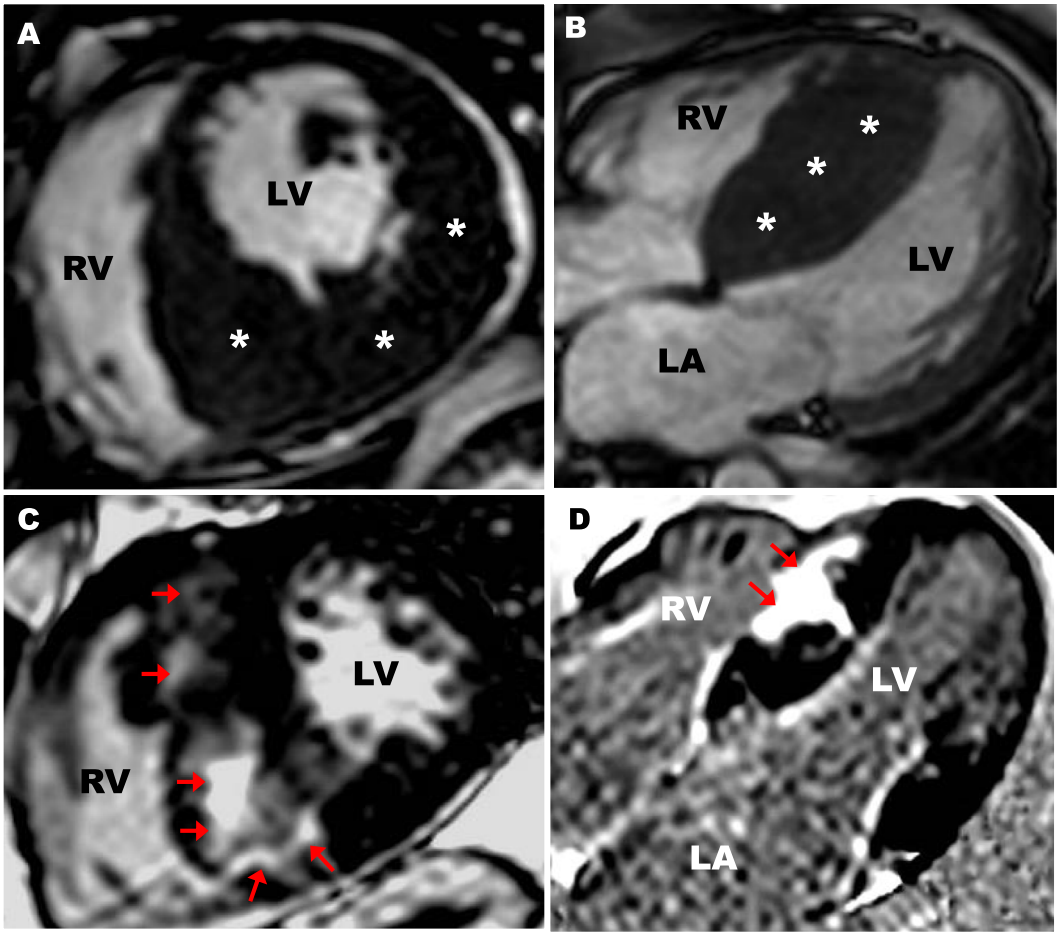

Figure 2. CMR images in end-diastole showing patterns of massive LV hypertrophy and late gadolinium enhancement. (A and B) Precontrast CMR images. (A) Hypertrophy isolated to basal posterior septum with extension into inferior and inferolateral walls (32 mm; asterisks); an asymptomatic nonobstructive 37-year-old man. (B) Hypertrophy involving septum (asterisks); 27-year-old man with advanced heart failure due to outflow obstruction who underwent successful surgical myectomy. (C and D) Contrast-enhanced CMR images demonstrating extensive LV scarring. (C) LGE evident throughout ventricular septum (arrows) occupying 20% of LV, with appropriate ICD shock for rapid VT 7 years after successful myectomy at age 19. (D) LGE (arrows), occupying 18% of LV myocardium; 39-year-old asymptomatic man with septal thickness of 30mm.
Abbreviations: LA = left atrium; LV = left ventricle; heart failure; RV = right ventricle.

HC-related deaths) was 100% and 92% (95% confidence interval: 70, 98%), no different from expected all-cause mortality in age-and gender-matched US population (standardized mortality ratio (SMR): 1.42; 95% confidence interval: 0.24, 4.69; log-rank p = 0.62; Figure 3).

Of 79 patients with primary prevention ICDs, 11 (14%) had aborted sudden death events with ≥1 ICD interventions terminating ventricular tachycardia/ventricular fibrillation (VT/VF) (2.8%/year; Supplemental table), including 2 patients with 2 interventions and one patient with 3. Initial ICD therapy occurred at age 34 ± 14 years, including 2 patients ≤20 years old and 2 patients >50 years old. Interval from implant to first ICD therapy was 6.3 ± 4.4 years (range, 0.5 to 13). The 11 patients have survived 4.4 ± 4.0 years (range to 10) after their event to age 38 ± 13 years, including 10 with no or mild symptoms.

Five patients were resuscitated from out-of-hospital cardiac arrest before initial visit to our institution (age 23 ± 11); 3 of these patients had 1 to 3 secondary prevention ICD interventions, after their event. Rate of aborted sudden death events in the 16 patients (3.0%/year) exceeded HC-related mortality 7-fold (0.4%/year; p <0.001). Sudden death events were 2.2-fold more common in patients presenting ≤35 years (n = 10 [20%]; 4.2%/year) than >35 years (n = 6 [14%]; 1.9%/year, p = 0.13, Figure 3).

Device-related complications occurred in 12 of the 84 patients with primary or secondary prevention ICDs (14%), including inappropriate shocks (n = 9), lead fractures (n = 2), and/or infection (n = 1). Four of these patients also had appropriate device interventions terminating VT/VF.

Among the 15 patients ≥16 years of age with arrhythmic sudden death events (appropriate ICD interventions and resuscitated cardiac arrest), 9 (60%) received low ESC risk scores (<4%/5years) insufficient for an ICD recommendation,[21] and would have remained exposed to sudden death risk.

Advanced drug-refractory heart failure symptoms (NYHA class III/IV) developed in 35 patients (38%) due to LV outflow tract obstruction at rest or with physiologic (exercise) provocation (gradient, 76 ± 20 mm Hg). These

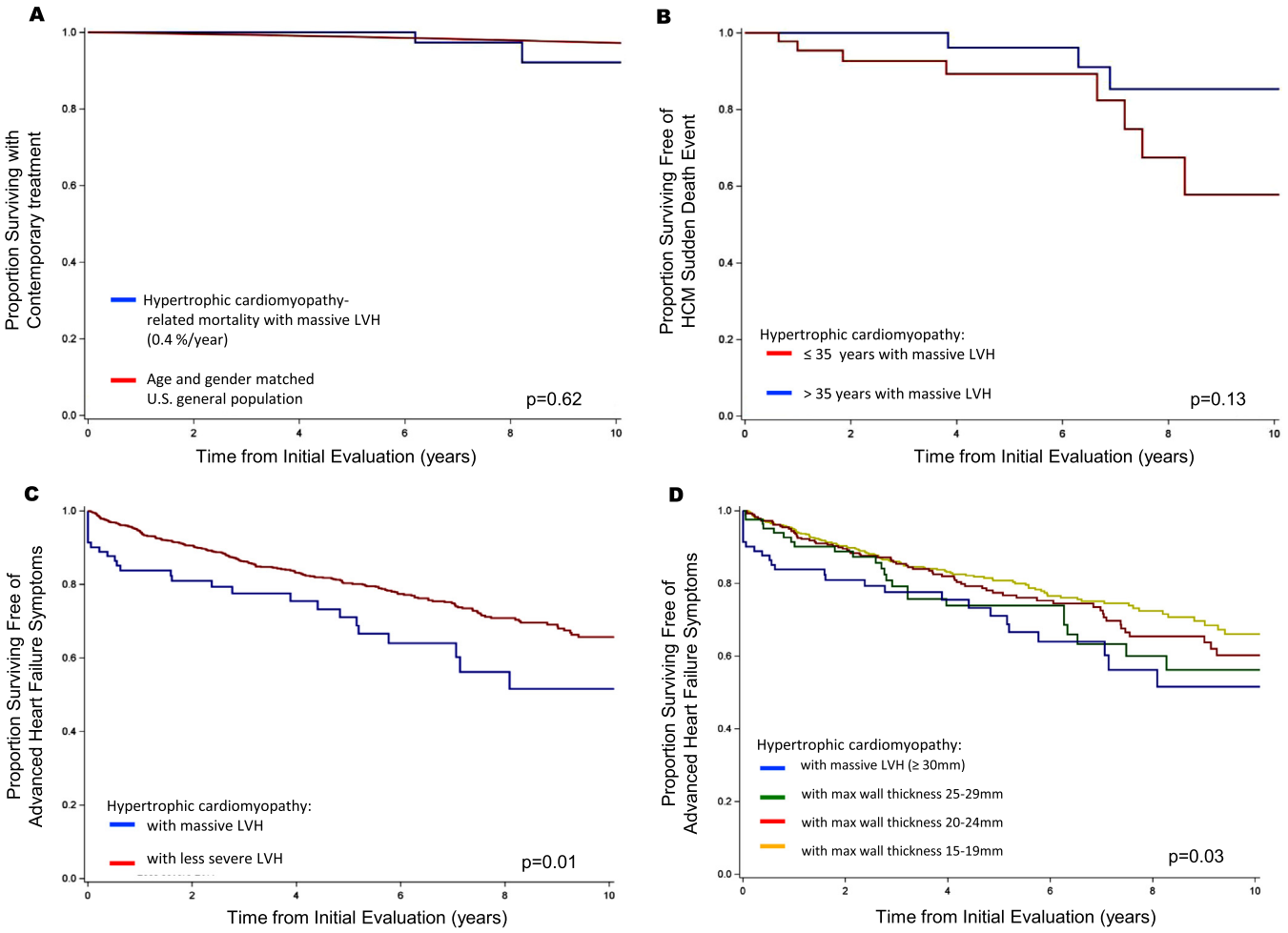

Figure 3. HC-related mortality and adverse HC-related events and survival by Kaplan-Meier analysis. (A) With contemporary treatment, HC mortality in 92 patients with massive LV hypertrophy does not differ from all-cause mortality in age and gender-matched general population; (B) Sudden death risk (aborted and nonfatal) in younger HC patients with massive hypertrophy patients (≤35 years) exceeds by 2-fold the rate in those patients >35 years, without achieving statistical significance; (C) Severe heart failure symptoms were more common in HC patients with massive LV hypertrophy than in patients with lesser LV hypertrophy. (D) Advanced heart failure symptoms were most common in patients with massive LV hypertrophy, but also increased progressively with respect to magnitude of LV wall thickness: 15 to 19 mm, 20 to 24 mm, and 25 to 29 mm.

patients underwent septal myectomy at age 35 ± 14 with relief of obstruction, and with no operative mortality. Of the 35 myectomy patients, 30 (86%) are alive, 3.8 ± 3.2 years postoperatively, and improved to NYHA classes I/II. The remaining 5 patients (14%) experienced persistent heart failure symptoms despite gradient relief, including 3 with ejection fraction <50% (one of whom has had a heart transplant). Most of the 541 patients undergoing myectomy experienced symptomatic response (95% with improvement to NYHA class I/II). However, massive hypertrophy patients more commonly had persistent symptoms (NYHA class III/IV) postmyectomy than did operated patients with less substantial hypertrophy (14% vs. 5%, p=0.01). Two other patients with massive hypertrophy without obstruction also developed advanced HF symptoms.

We made comparisons of the 92 patients with massive LV hypertrophy to the 1674 HC patients with lesser magnitude of hypertrophy (Table 2). Patients with massive hypertrophy had significantly higher sudden death event rates (3.0%/year vs. 0.8%/year, p<0.001; Figure 4) which occurred at younger ages in patients with massive LV hypertrophy (30 ± 13 vs 46 ± 17 with less hypertrophy; p <0.001).

For example, the 92 patients with massive LV hypertrophy more commonly had resting LV outflow obstruction (≥30 mm Hg; 50% vs 37%; p = 0.01) and higher rates of heart failure progression to NYHA classes III/IV (5.8%/year vs 4.0%/year, p = 0.01; Figure 3). Heart failure progression increased in frequency across LV hypertrophy quartiles from 15 to 19 mm (3.8%/year), 20 to 24 mm (4.6%/year), 25 to 29 mm (5.2%/year), >30 mm (5.8%/year, p = 0.03) (Figure 3). HC-related mortality in the 92 patients with massive LV hypertrophy (0.4%/year) did not differ from the 1,674 patients with lesser hypertrophy (0.3%/year, p = 0.71), and was similar across all hypertrophy quartiles (0.3%/year to 0.4%/year, p = 0.62).

DISCUSSION

Patients with the most extreme increases in LV mass represent a relatively small but highly visible and important

Table 2
Clinical demographics and outcomes of hypertrophic cardiomyopathy patients by subgroups of maximum LV wall thickness

Variable	LV wall thickness (mm)			
	15-19 (n = 918)	20-24 (n = 417)	25-29 (n = 127)	≥30 (n = 92)
Males	565 (62%)	299 (63%)	80 (62%)	65 (71%)
Age at initial evaluation (years)	54 ± 16	53 ± 16	48 ± 17	33 ± 14
Age diagnosis (years)	48 ± 17	46 ± 18	40 ± 17	26 ± 13
Age most recent evaluation (years)	58 ± 16	58 ± 16	54 ± 17	38 ± 14
Maximum LV thickness (mm)	17 ± 1	22 ± 1	26 ± 1	32 ± 3
Ejection fraction (%)	63 ± 6	64 ± 6	65 ± 5	66 ± 4
Left atrial dimension (mm)	41 ± 7	43 ± 7	44 ± 7	42 ± 8
LVED (mm)	42 ± 7	42 ± 7	41 ± 7	40 ± 6
LVOT gradient, ≥30 mm Hg at rest	327 (36%)	222 (47%)	57 (45%)	46 (50%)
LVOT gradient, <30 mm Hg at rest and ≥50 mm Hg-exercise	164 (18%)	73 (15%)	12 (9%)	9 (10%)
Family history of HC	197 (21%)	121 (26%)	38 (30%)	40 (43%)
Family history HC-related death	85 (9%)	50 (11%)	16 (13%)	24 (26%)
Unexplained syncope	106 (12%)	55 (12%)	25 (20%)	20 (22%)
Nonsustained ventricular tachycardia on ambulatory Holter-monitor	139 (15%)	87 (18%)	27 (21%)	26 (28%)
Contrast-CMR				
Number CMR studies	651	273	62	42
Number with late gadolinium enhancement, %	332 (51%)	205 (75%)	50 (81%)	40 (95%)
% late gadolinium enhancement	4.9 ± 5.6	6.1 ± 5.4	9.3 ± 6.4	8.9 ± 5.2
Number with late gadolinium enhancement ≥ 15% of LV	19 (6%)	15 (7%)	9 (18%)	9 (19%)
NYHA-FC, initial evaluation				
I	368 (40%)	152 (32%)	45 (35%)	35 (38%)
II	256 (28%)	123 (26%)	36 (28%)	35 (40%)
III/IV	294 (32%)	196 (41%)	46 (36%)	20 (22%)
Number patients with ICDs	195 (21%)	127 (27%)	60 (47%)	84 (91%)
Number with aborted sudden death events	42 (5%)	24 (5%)	13 (10%)	16 (17%)
Appropriate ICD Interventions	33 (4%)	19 (4%)	13 (10%)	14*(15%)
Resuscitated cardiac arrest	13 (1%)	9 (2%)	1 (1%)	5* (5%)
Septal myectomy	269 (29%)	174 (37%)	44 (34%)	35 (38%)
Postoperative NYHA-FC class I/II	251 (94%)	164 (96%)	44 (100%)	30 (86%)
Postoperative NYHA-FC class III/IV	15 (6%)	7 (4%)	0 (0%)	5 (14%)
Alcohol septal ablation	67 (7%)	49 (10%)	14 (11%)	1‡ (1%)
Heart transplant	14 (2%)	13 (3%)	2 (2%)	1 (1%)
NYHA-FC, last evaluation				
I	485 (59%)	249 (58%)	63 (55%)	50 (57%)
II	298 (37%)	143 (33%)	43 (38%)	33 (37%)
III/IV	51 (6%)	31 (7%)	7 (6%)	5 (6%)
Deaths	67 (7%)	41 (9%)	13 (10%)	4 (4%)
Non-HCM death	55 (6%)	31 (7%)	12 (9%)	2†† (2%)
HCM-related death	12 (1%)	10 (2%)	1 (1%)	2 (2%)

subgroup of HC patients,[25] generally regarded as having the most malignant form of the disease with increased risk for early complications, including sudden death.[4–8] A relevant issue addressed in this study concerns whether management principles utilized in other high risk HC patients are as effective in patients with extreme presentation of the disease.[1–3]

In this tertiary referral population, we confirmed that patients with massive LV hypertrophy are at increased risk for sudden death as well as the development of drug refractory heart failure symptoms secondary to LV outflow obstruction. Nevertheless, we found that contemporary treatment interventions available to HC patients such as ICDs, external defibrillation, and surgical myectomy led to prevention of sudden death and reversal of advanced heart failure symptoms due to outflow obstruction. As a consequence of these therapeutic strategies in vulnerable patients we are able to report a low HC-related mortality rate of 0.4%/year, no different than our HC patients with less substantial hypertrophy, and consistent with that reported in other HC patient subgroups.[1–3]

About 15% of our patients with extreme LV hypertrophy have, to date, benefited from risk stratification and prophylactically implanted ICDs with appropriate device therapy for potentially lethal ventricular tachyarrhythmias and associated with a low rate of device complications. Furthermore, our event rate of 3% is similar to that reported in other high risk HC subgroups in registry populations,[15–17] and is substantially higher than that of HC patients with less substantial hypertrophy in the comparison cohort. Also, given the relatively youthful age of our patients it is likely that additional individuals will emerge over time with life-saving ICD interventions.[2] Indeed, ICD therapy has already occurred in the present study group up to 13 years after prophylactic device implantation (including to age 57), and delays of >10 years have also been reported in other studies of HC patients, including in some with massive LV hypertrophy.[15–17]

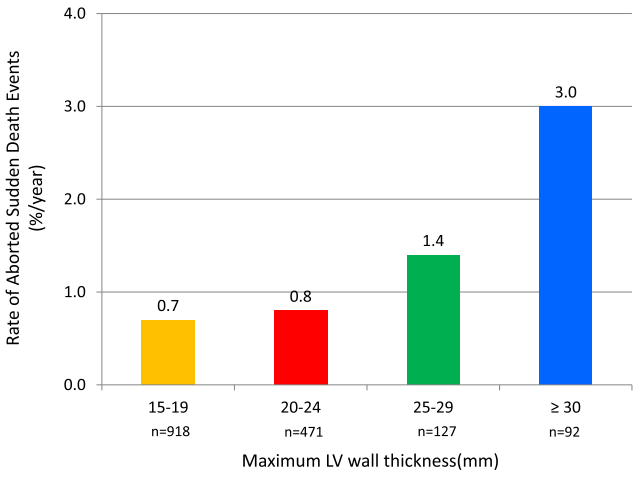

Figure 4. Progressive increase in rate of aborted sudden death events in HC cohort of 1,766 patients, significantly greater rate ($p < 0.001$) for those with massive LV hypertrophy (wall thickness ≥ 30 mm).

Sudden death events were more common in younger patients with extreme LV hypertrophy (≤35 years of age), but contrary to other HC studies we found that sudden death risk in patients with massive hypertrophy persisted into midlife.[4,5,26] Indeed, about 15% of our patients >35 years of age experienced appropriate device therapy for VT/VF, underscoring the importance of prudently considering prophylactic ICDs in this age group. However, our data do not resolve whether such decision-making should be extended to patients of relatively advanced ages >60 years with extreme hypertrophy, given the small number of such patients in the present cohort.[27]

Although survival into midlife and beyond was once considered unlikely for HC patients with extreme LV hypertrophy,[4,5,7,8] our data support the principle that with contemporary treatment options, these patients can experience extended longevity. Indeed, almost 25% of our patients have survived to ≥50 years of age (up to 70), each with no or only mild symptoms.

There has also been a measure of concern that defibrillation shocks may not reliably terminate malignant arrhythmias in HC patients with extreme increase in LV mass.[6,15–17] However, our data clearly dispel that notion, since not only have all 16 patients with appropriate device interventions (including some with multiple shocks) survived >5 years (and up to 10 years) after their first ICD intervention, but the vast majority are experiencing favorable quality of life with no or few symptoms.

In contrast to another report,[18] we found sudden death risk increased and ICDs to be effective in those patients with the most profound degree of hypertrophy (LV wall thickness ≥ 35 mm), with 25% of such patients experiencing effectively terminated arrhythmic sudden death events by ICDs. Therefore, the inverted U-shaped relation between extreme LV wall thickness and sudden death risk proposed by O'Mahoney et al,[20] does not appear to be a reliable sudden death marker applicable to HC.

In addition, refractory heart failure symptoms and disability consistent with NYHA class III was relatively common, occurring in 40% of massive hypertrophy patients with obstruction, and at higher rates than in patients with less substantial hypertrophy. The vast majority of these patients were successfully treated with surgical myectomy and relief of outflow obstruction leading to substantial symptomatic improvement in over 85%[9–14], without operative mortality.

Notably, 6 myectomy patients also had appropriate ICD interventions or resuscitated cardiac arrest, and therefore represent a particularly aggressive subset with the coexistence of 2 adverse (but treatable) disease pathways, that is, prevention of arrhythmic sudden death and heart failure reversal.[28] In contrast, we should underscore that referral patterns in this study may have unavoidably underestimated patients with benign clinical course, potentially leading to a disproportionately increased proportion of patients with advanced heart failure, including those referred to the robust surgical myectomy program at Tufts Medical Center.[13]

Furthermore, clinical course of nonobstructive patients with extreme hypertrophy was largely favorable with >90% experiencing no or only mild symptoms over follow-up, consistent with our observations in larger and more diverse nonobstructive HC cohorts with less substantial hypertrophy. However, a small number of relatively young patients with massive hypertrophy developed progressive and unrelenting heart failure, and ultimately became heart transplant candidates.[29,30]

Finally, our data demonstrate that the mathematical risk score promoted by ESC is particularly unreliable in identifying high risk HC patients with extreme degrees of LV hypertrophy.[18,21,24] Indeed, two-thirds of our high risk patients with massive hypertrophy and life-threatening VT/VF events had low ESC risk scores (<4%/5 years) which would have excluded an ICD recommendation.[21] Using only the ESC score to assess risk, these patients would have remained vulnerable to arrhythmic sudden death.

In conclusion, our data expand the principle that HC can be effectively treated in young patients with the most extreme morphologic form of this disease. We have demonstrated in the present cohort that patients with massive LV hypertrophy are at substantially increased risk for malignant ventricular tachyarrhythmias compared to patients with less marked hypertrophy. Primary prevention ICDs effectively prevented sudden death by terminating VT/VF even in the presence of greatly increased LV mass. Notably, the ESC risk score was unreliable in identifying patients at risk for arrhythmic sudden death and should be avoided in ICD decision-making for patients with massive hypertrophy. Furthermore, surgical myectomy was effective in relieving outflow obstruction and heart failure symptoms in most patients. Therefore, with the advantage of contemporary treatment options, young HC patients with extreme disease expression can also aspire to longevity with good quality of life.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.002.

1. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med* 2018;379:655–668.
2. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol* 2015;65:1915–1928.
3. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. *Circulation* 2016;133:62–73.
4. Olivotto I, Gistri R, Petrone P, Pedemonte E, Vargiu D, Cecchi F. Maximum left ventricular thickness and risk of sudden death in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;41:315–321.
5. Sorajja P, Nishimura RA, Ommen SR, Ackerman MJ, Tajik AJ, Gersh BJ. Use of echocardiography in patients with hypertrophic cardiomyopathy: clinical implications of massive hypertrophy. *J Am Soc Echocardiogr* 2006;19:788–795.
6. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:1778–1785.
7. Maron MS, Zenovich AG, Casey SA, Link MS, Udelson JE, Aeppli DM, Maron BJ. Significance and relation between magnitude of left ventricular hypertrophy and heart failure symptoms in hypertrophic cardiomyopathy. *Am J Cardiol* 2005;95:1329–1333.
8. Thaman R, Gimeno JR, Reith S, Esteban MT, Limongelli G, Murphy RT, Mist B, McKenna WJ, Elliott PM. Progressive left ventricular remodeling in patients with hypertrophic cardiomyopathy and severe left ventricular hypertrophy. *J Am Coll Cardiol* 2004;44:398–405.
9. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;46:470–476.
10. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, Lever HM. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circulation* 2013;128:209–216.
11. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, Siu S, Ralph-Edwards A, Rakowski H. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation* 2005;111:2033–2041.
12. Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. *J Am Coll Cardiol* 2016;67:1846–1858.
13. Rastegar H, Boll G, Rowin EJ, Dolan N, Carroll C, Udelson JE, Wang W, Carpino P, Maron BJ, Maron MS, Chen FY. Results of surgical septal myectomy for obstructive hypertrophic cardiomyopathy: the Tufts experience. *Ann Cardiothorac Surg* 2017;6:353–363.
14. Brown ML, Schaff HV, Dearani JA, Li Z, Nishimura RA, Ommen SR. Relationship between left ventricular mass, wall thickness, and survival after subaortic septal myectomy for hypertrophic obstructive cardiomyopathy. *J Thorac Cardiovasc Surg* 2011;141:439–443.
15. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA 3rd, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007;298:405–412.
16. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, 3rd ENA, Shannon KM, Ashley EA, Day SM, Pacileo G, Formisano F, Devoto E, Anastasakis A, Bos JM, Woo A, Autore C, Pass RH, Boriani G, Garberich RF, Almquist AK, Russell MW, Boni L, Berger S, Maron MS, Link MS. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;61:1527–1535.
17. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. *Circ Heart Fail* 2012;5:552–559.
18. O'Mahony C, Jichi F, Monserrat L, Ortiz-Genga M, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM. Inverted U-Shaped relation between the risk of sudden cardiac death and maximal left ventricular wall thickness in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol* 2016:9. https://doi.org/10.1161/CIRCEP.115.003818. pii: e003818.
19. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *Circulation* 2011;124:e783–e831.
20. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;42:1687–1713.
21. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J* 2014;35:2733–2779.
22. Maron MS, Rowin EJ, Olivotto I, Casey SA, Arretini A, Tomberli B, Garberich RF, Link MS, Chan RHM, Lesser JR, Maron BJ. Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2016;67:1399–1409.
23. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;130:484–495.
24. O'Mahony C, Jichi F, Pavlou M, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin EJ, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HC risk-SCD). *Eur Heart J* 2014;35:2010–2020.
25. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, Maron MS. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. *J Am Coll Cardiol* 2017;69:761–773.
26. Maron BJ, Piccininno M, Casey SA, Bernabo P, Spirito P. Relation of extreme left ventricular hypertrophy to age in hypertrophic cardiomyopathy. *Am J Cardiol* 2003;91:626–628.
27. Maron BJ, Rowin EJ, Casey SA, Haas TS, Chan RH, Udelson JE, Garberich RF, Lesser JR, Appelbaum E, Manning WJ, Maron MS. Risk stratification and outcome of patients with hypertrophic cardiomyopathy $\geq$ 60 years of age. *Circulation* 2013;127:585–593.
28. Rowin EJ, Maron MS, Chan RH, Hausvater A, Wang W, Rastegar H, Maron BJ. Interaction of adverse disease related pathways in hypertrophic cardiomyopathy. *Am J Cardiol* 2017;120:2256–2264.
29. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006;114:216–225.
30. Rowin EJ, Maron BJ, Abt P, Kiernan MS, Vest A, Costantino F, Maron MS, DeNofrio D. Impact of advanced therapies for improving survival to heart transplant in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2018;121:986–996.