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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Major Cardiac Events in Patients and Relatives With Hereditary Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Little evidence is available on the disease expression in relatives of index patients with hypertrophic cardiomyopathy (HCM). This information has important implications for family screening programs, genetic counseling, and management of affected families.

OBJECTIVES The purpose of this study was to investigate the disease expression and penetrance in relatives of index patients carrying pathogenic/likely pathogenic (P/LP) variants in recognized HCM genes.

METHODS A total of 453 consecutive and unrelated HCM index patients underwent clinical and genetic investigations. A total of 903 relatives of genotype-positive index patients were invited for clinical investigations and genetic testing. Penetrance, disease expression, and incidence rates of major adverse cardiac events (MACEs) were investigated in individuals carrying P/LP variants.

RESULTS Forty percent (183/453) of index patients carried a P/LP variant. Eighty-four percent (757/903) of all relatives of index patients with P/LP variants were available for the investigation, of whom 54% (407/757) carried a P/LP variant. The penetrance of HCM among relatives was 39% (160/407). Relatives with HCM and index patients were diagnosed at a similar age (43 $\pm$ 18 years vs 46 $\pm$ 15 years; $P = 0.11$). There were no differences in clinical characteristics or incidence rates of MACE during 8 years of follow-up.

CONCLUSIONS The disease expression of HCM among index patients and affected relatives carrying P/LP variants in recognized disease genes was similar, with an equal risk of experiencing MACE. These findings provide evidence to support family screening and follow-up of genotype-positive HCM families to improve management and diminish the number of adverse disease complications among relatives. (JACC Adv 2023;2:100604) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

HCM = hypertrophic cardiomyopathy

HCP = high confidence pathogenic

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVH = left ventricular hypertrophy

MACE = major adverse cardiac event(s)

P/LP = pathogenic/likely pathogenic

SCD = sudden cardiac death

Hypertrophic cardiomyopathy (HCM) is a common hereditary cardiac condition that affects approximately 1:500 and may be associated with severe disease complications, including sudden cardiac death (SCD), endstage heart failure, and disabling stroke.[1-3] Due to the hereditary nature of the disease, current guidelines recommend clinical investigations of relatives at risk of having inherited the disease.[1,4] So far, only a few studies have investigated the disease expression, penetrance, and number of major adverse cardiac events (MACEs) among relatives of HCM index patients carrying pathogenic and likely pathogenic sequence variants (P/LP variants).[5-7] The results of these investigations have suggested that genotype-positive relatives have a fairly mild disease expression, although little data has been available to support the findings reported.

The aim of the current study was to characterize the disease expression in a large consecutive cohort of genotype-positive HCM families and compare the disease expression among index patients and affected relatives. Thereby, it would be possible to provide a firm basis for recommendations regarding family screening programs and follow-up.

METHODS

STUDY DESIGN AND STUDY POPULATION. This investigation represents a multicenter, longitudinal cohort study of consecutive and unrelated HCM index patients and their relatives at risk of developing the condition.

All index patients underwent genetic investigations in recognized HCM genes and were eligible for the study once they were shown to carry a P/LP variant according to the American College of Medical Genetics and Genomics criteria.[8] They were all followed at specialized units for inherited cardiovascular conditions at 5 tertiary referral hospitals in Denmark between 1987 and 2020. The combined catchment area of these centers represented 54% (3,144,788/5,837,213) of the Danish population in 2020.[9]

Relatives at risk of having inherited P/LP variants of the index patient were invited for genetic testing via the index patient and offered a cardiac evaluation, which included a physical examination, 12-lead electrocardiography recording, and transthoracic echocardiography (TTE).

Asymptomatic children below the age of 10 were invited for clinical and genetic investigation in families with a history of early-onset HCM. Information about deceased HCM index patients and relatives was obtained from hospital notes and autopsy records.

The study complied with the Declaration of Helsinki and was approved by the Danish data protection agency (15/32566). Informed written consent was obtained from all participants. Data supporting the study's findings will be made available upon reasonable request for purposes of reproducing the results or replicating the procedures.

HCM DIAGNOSTIC CRITERIA. HCM was defined by the presence of unexplained left ventricular hypertrophy (LVH) with a wall thickness ≥15 mm by echocardiography or cardiac magnetic resonance imaging, which was not explained solely by abnormal loading conditions, in accordance with European Society of Cardiology (ESC) guidelines.[1]

Relatives older than 18 years of age received a diagnosis of HCM in the presence of LVH ≥13 mm in the absence of abnormal loading conditions. Children ≤18 years of age received a diagnosis of HCM when they presented with LVH of more than 2 standard deviations of the predicted mean.[1,10]

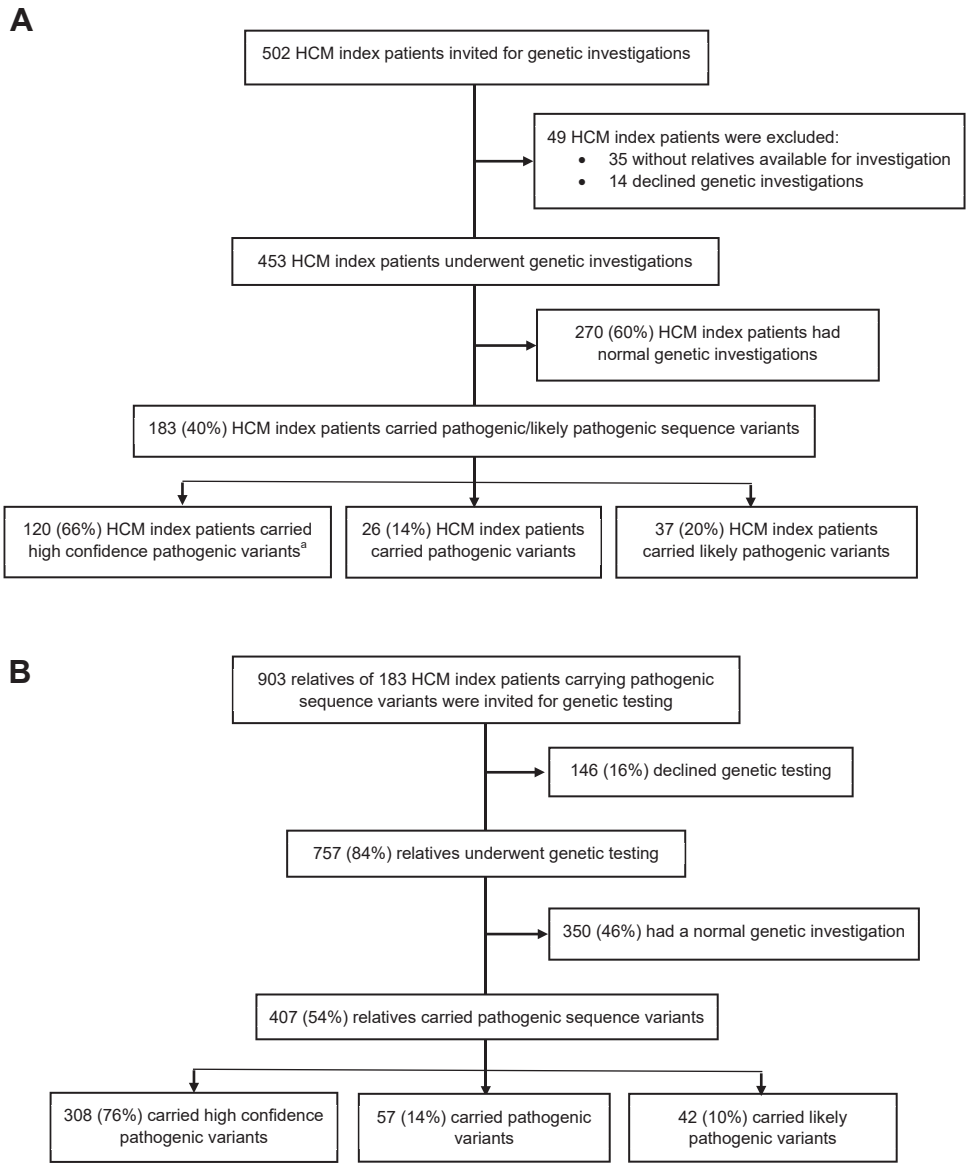
Relatives younger than 50 years of age who died from SCD were assumed to have HCM if they carried a P/LP variant or were obligate carriers of the P/LP variant in the family.

GENETIC INVESTIGATIONS. All HCM index patients underwent genetic investigation by next-generation sequencing of 106 recognized and likely HCM genes by use of Illumina Hiseq next-generation sequencing technology, as reported previously and in Supplemental Table 1.[11,12] Once a likely P or LP sequence variant was identified in an index patient, predictive genetic testing of the specific variant in relatives was performed by Sanger sequencing.

Variants were considered to be of sufficient high confidence and suitable for predictive genetic testing when they: 1) fulfilled the criteria of being likely pathogenic/pathogenic by American College of Medical Genetics and Genomics; 2) appeared in ≥7 individuals fulfilling HCM diagnostic criteria; and 3) occurred with an allele frequency <1:25.000 in the Genome Aggregation Database.[13,14]

ECHOCARDIOGRAPHY. All individuals underwent standard 2-dimensional transthoracic echocardiographic evaluation, which included measurement of the maximal wall thickness, left atrial size, left ventricular (LV) ejection fraction, and LV outflow tract gradient. Maximal wall thickness was determined as the maximal thickness of the LV wall in any segment. Peak outflow tract gradient was determined from

FIGURE 1 Results of Genetic Investigations of HCM Index Patients and Their Relatives



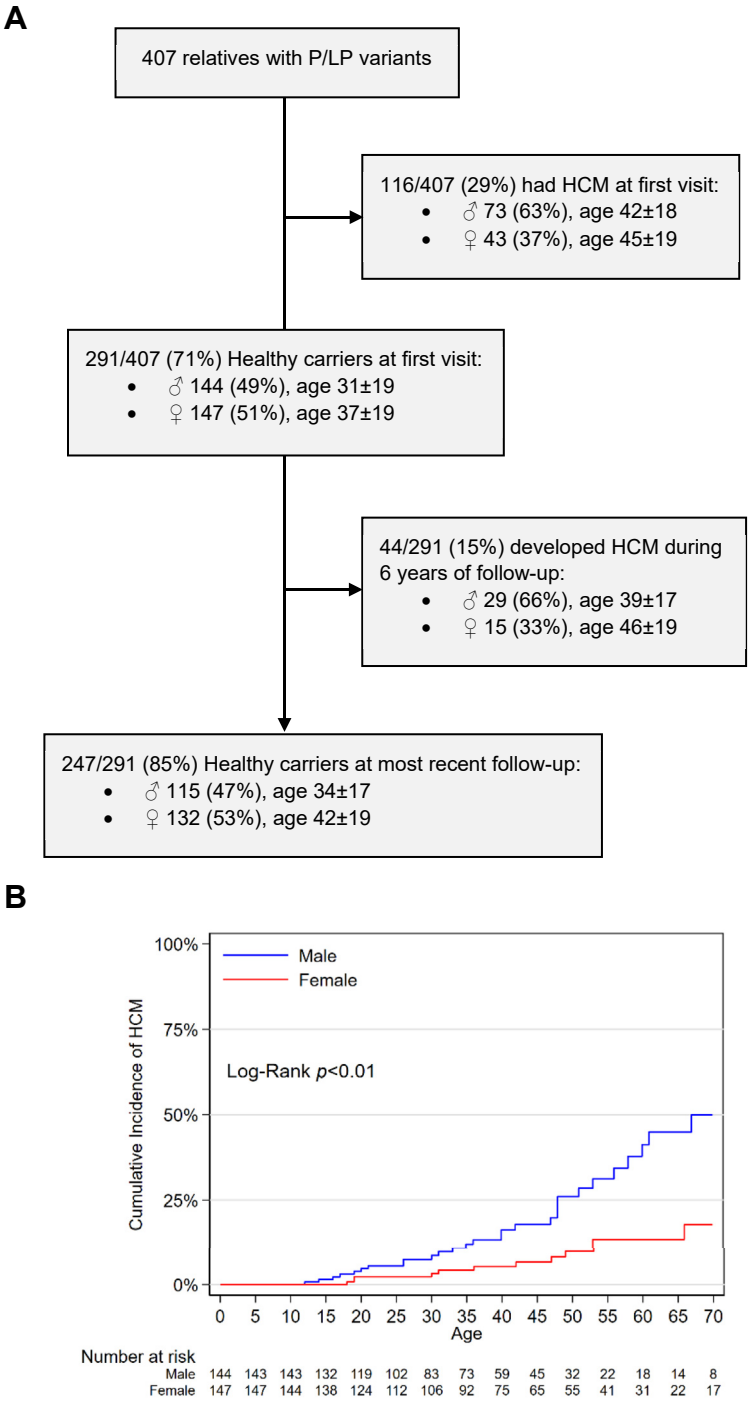
(A) Genetic investigation of 453 index patients identified pathogenic/likely pathogenic variants (P/LP) in 40% (183/453) of index patients. (B) Genetic testing in 757 relatives of P/LP sequence variants identified in 183 HCM index patients showed that 407 (54%) relatives carried a P/LP variant. [a]High confidence pathogenic variants were defined as a pathogenic (P)/likely pathogenic (LP) sequence variant according to ACMG classification and, in addition, appeared with a frequency of <1:25,000 in the genome aggregation database and present in ≥7 affected individuals. ACMG = American College of Medical Genetics and Genomics; HCM = hypertrophic cardiomyopathy.

pulsed and continuous wave Doppler and derived from the modified Bernoulli equation. LV outflow tract obstruction was defined as a gradient ≥30 mmHg at rest or following provocation with Valsalva maneuver.[1]

ELECTROCARDIOGRAM. A 12-lead electrocardiography was recorded at all visits and analyzed for abnormalities. LVH pattern was based on Sokolow-Lyon criteria (SV1 + RV5/6 > 35 mV), and Q-waves were considered abnormal if they were >40 ms wide, >2 mm deep, >25% of the depth of QRS complex, or if present in leads V_1-V_3 except lead III and aVR.

STUDY OUTCOME AND DEFINITIONS. MACEs were defined as a composite endpoint of disabling stroke,

FIGURE 2 Penetrance of HCM Among Relatives Carrying P/LP Variants



Penetrance of HCM among carriers of P/LP variants during follow-up. (A) Result of clinical investigation of 407 carriers. At the first visit, 29% (116/407) were diagnosed with HCM, while 15% (44/291) developed HCM during a median of 6 years of follow-up. (B) Penetrance of HCM during a median follow-up of 6 years (IQR: 3-10 years) is shown for males and females according to age. HCM = hypertrophic cardiomyopathy; P/LP = pathogenic/likely pathogenic variants.

heart transplantation, death from heart failure, and SCD. The incidence of MACE was determined from the time of diagnosis to the end of the study (January 2021). SCD was defined as a natural and unexpected death.[15] Appropriate implantable cardioverter-defibrillator (ICD) shock therapy and successful resuscitation from ventricular fibrillation or ventricular tachycardia were considered to be equivalent to SCD.[16]

STATISTICAL ANALYSIS. Statistical analyses were performed using STATA/IC version 16.0. Symmetrically distributed continuous data are expressed as mean ± SD, skewed data as median (IQR), and categorical variables as counts or percentages. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. Kruskal-Wallis was used for variables with more than 2 groups. A paired test and the Wilcoxon signed-rank test were used to compare symmetrically and skewedly distributed continuous data. Kaplan-Meier methods were used for survival analysis. Age of diagnosis of HCM or age at the most recent follow-up was used to estimate the age-dependent penetrance of HCM. For event-free survival analysis of HCM index patients and affected relatives, the follow-up period in years was used to estimate time from diagnosis to the occurrence of a MACE or if no MACE appeared until the most recent follow-up. Groups were compared using the log-rank test. A 2-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

GENETIC INVESTIGATIONS. HCM index patients. Unrelated HCM index patients (n = 502) were invited for genetic investigations, of whom 453 (90%) accepted the invitation (**Figure 1A**). Forty percent (183/453) were shown to carry a P/LP variant, which was most frequently identified in the genes for *MYBPC3* (15%), *MYH7* (7.5%), *TNNI3* (3.5%), and *TPM1* (3.0%) (Supplemental Figure 1). In total, 183 index patients were shown to carry 103 different P/LP variants. Forty-nine percent of these (50/103) were considered to be high-confidence pathogenic variants suitable for predictive genetic testing since they were present in at least 7 affected individuals based on the current investigation and previous reports.

Relatives of HCM index patients carrying P/LP variants. Relatives of 183 HCM index patients carrying P/LP variants (n = 903) were offered genetic testing, of whom 84% (757/903) accepted the invitation (**Figure 1B**). Fifty-four percent (407/757) of these relatives carried a P/LP variant, of whom 76% (308/407) carried a high-confidence pathogenic variant.

PENETRANCE OF HCM AMONG RELATIVES CARRYING P/LP VARIANTS. The penetrance of HCM among relatives was 39% (160/407), of whom 29% (116/407) were diagnosed with HCM at their first visit at an average age of 42 ± 18 years for males and 45 ± 19 years for females ($P = 0.40$). Fifteen percent (44/[407−116 = 291]) of the remaining relatives developed HCM during a median follow-up of 6 years (IQR: 3-10 years), at an average age of 39 ± 17 years for males and 46 ± 19 years for females ($P = 0.20$) (**Figure 2A**).

The penetrance of HCM during follow-up was significantly higher in male carriers (HR: 2.5 [95% CI: 1.4-2.7], $P < 0.01$) (**Figure 2B**). In addition, both male and female variant carriers above 50 years of age had a significantly higher hazard ratio of penetrance compared to carriers within the age groups 0 to 24 years (HR: 4.3 [95% CI: 2.0-9.7], $P < 0.01$) (Supplemental Table 2).

CLINICAL CHARACTERISTICS OF INDEX PATIENTS AND RELATIVES WITH HCM. The average age at time of diagnosis was the same for index patients and affected relatives (46 ± 15 years vs 43 ± 18 years; $P = 0.10$) (**Table 1**). There was no significant difference in the sex distribution between index patients and affected relatives (males: n = 99; 54% vs n = 102; 64%; $P = 0.1$).

Information about symptoms and LV outflow tract obstruction at the time of diagnosis was available in 91% (166/183) of index patients and 90% (141/160) of affected relatives. Seventy percent (116/166) of index patients were diagnosed due to symptoms including shortness of breath, angina, palpitations, or syncope, while significantly fewer relatives experienced symptoms at the time of diagnosis (45% [63/141]; $P < 0.01$). Index patients had more pronounced LVH (20 mm vs 16 mm; $P < 0.01$) and a higher frequency of LV outflow tract obstruction (n = 37; 22% vs n = 8; 6%; $P < 0.01$) than their affected relatives.

Information about pharmacological treatment and invasive procedures during follow-up was available for 97% (177/183) of index patients and 93% (149/160) of affected relatives. Throughout the study period, index patients were more likely to receive medical treatment for HCM compared to affected relatives, which included beta-blockers (n = 114; 64% vs n = 46; 31%; $P < 0.01$), ACE/ARB (n = 37; 21% vs n = 12; 8%; $P < 0.01$), diuretics (n = 43; 24% vs n = 14; 9%; $P < 0.01$), and anticoagulants (n = 50; 28% vs n = 22; 15%; $P < 0.01$). In addition, percutaneous septal alcohol ablation as well as

TABLE 1 Clinical Characteristics of HCM Index Patients and Relatives Carrying Pathogenic Variants

	Index Patients (n = 183)	Relatives With HCM (n = 160)	*P* Value[d]	Relatives Without HCM (n = 247)	*P* Value[e]
Demographic data					
Age (y)[a]	46 ± 15	43 ± 18	0.11	38 ± 18	0.02
Male	99 (54.1%)	102 (63.7%)	0.07	115 (46.6%)	<0.01
Comorbidity[a]					
Hypertension	34/168 (19.1%)	18/139 (12.9%)	0.14	22/185 (11.9%)	0.77
AF	50 (27.3%)	24 (15.0%)	<0.01	7/185 (3.8%)	<0.01
Diabetes	10/178 (5.6%)	9/113 (8.0%)	0.44	8/183 (4.4%)	0.20
COPD	13/178 (7.3%)	1/113 (0.9%)	0.01	4/183 (2.2%)	0.40
Ischemic heart disease	9/165 (5.5%)	9/139 (6.5%)	0.72	-	-
Clinical evaluation[a]	(n = 166)	(n = 141)		(n = 227)	
Cardiac symptoms	116 (69.9%)	63 (44.7%)	<0.01	17 (7.5%)	<0.01
NYHA functional class II	55 (33.1%)	30 (21.3%)	0.06	7 (3.1%)	<0.01
NYHA functional class III	2 (1.2%)	3 (2.1%)		-	
Angina	37 (22.3%)	19 (13.5%)	0.04	3 (1.3%)	<0.01
Syncope	30 (18.1%)	4 (2.8%)	<0.01	2 (0.9%)	0.15
Palpitations	35 (21.1%)	28 (19.9%)	0.77	6 (2.6%)	<0.01
ECG evaluation[a]	(n = 161)	(n = 139)		(n = 224)	
Abnormal ECG	141 (87.6%)	117 (84.2%)	0.41	22 (9.8%)	<0.01
AF	3 (1.6%)	6 (3.8%)	0.22	1 (0.4%)	<0.01
LVH pattern	101 (62.7%)	71 (50.7%)	0.04	10 (4.5%)	<0.01
Abnormal repolarization	97 (60.2%)	85 (61.2%)	0.8	10 (4.5%)	<0.01
Abnormal Q waves	18 (11.2%)	32 (23.0%)	0.01	4 (1.8%)	<0.01
Echocardiographic evaluation[a]					
MWT (mm)	20 (16-23)	16 (14-19)	<0.01	10 (10-10)	<0.01
ASH	135/160 (84.4%)	113/136 (83.1%)	0.19	-	-
Apical	18/160 (11.3%)	14/136 (10.3%)		-	-
Lateral	2/160 (1.3%)	4/136 (2.9%)		-	-
Concentric	5/160 (3.1%)	5/136 (3.7%)		-	-
LVOT obstruction	37/166 (22.3%)	8/141 (5.7%)	<0.01	-	-
Medical treatment during follow-up	(n = 177)	(n = 149)			
Beta-blockers	114 (64.4%)	46 (30.8%)	<0.01		
Calcium antagonist	20 (11.3%)	14 (9.4%)	0.58		
ACE/ARB	37 (20.9%)	12 (8.1%)	<0.01		
Diuretics	43 (24.3%)	14 (9.4%)	<0.01		
Warfarin/DOAC[b]	50 (28.2%)	22 (14.8%)	<0.01		
Invasive procedures during follow-up	(n = 177)	(n = 149)			
TASH	21 (11.9%)	6 (4.0%)	0.01		
Myectomy	9 (5.1%)	2 (1.3%)	0.06		
ICD for primary prevention[c]	69 (39.0%)	25 (16.8%)	<0.01		
ICD for secondary prevention[c]	9 (5.1%)	3 (2.0%)	0.14		

Values are mean ± SD, n (%), n/N (%), or median (IQR). [a]For HCM index patients and relatives with HCM, variables are from the first visit at diagnosis. For relatives without HCM, variables are from the most recent visit. [b]7 patients (10%) were treated with Warfarin, while 62 patients (90%) received DOAC. [c]ICDs for primary prevention were implanted in patients at risk of SCD in accordance with European Society of Cardiology guidelines. ICD for secondary prevention was implanted in survivors of a cardiac arrest or in patients with documented episodes of VF/VT. [d]Comparing index patients vs relatives with HCM. [e]Comparing relatives with HCM vs relatives without HCM.

ACE/ARB = angiotensin-converting enzyme inhibitors/angiotension II receptor blockers; AF = atrial fibrillation; Apical = predominately apical ventricular wall hypertrophy; ASH = asymmetrical septal hypertrophy; Concentric = concentric left ventricular wall hypertrophy; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulants; ECG = electrocardiography; HCM = hypertrophic cardiomyopathy; HF = heart failure; HTX = heart transplantation; ICD = implantable cardioverter-defibrillator; Lateral = predominately lateral ventricular wall hypertrophy; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; MWT = maximal wall thickness; SCD = sudden cardiac death; TASH = transcoronary ablation of septal hypertrophy.

myectomy was performed most frequently in index patients (n = 30; 17% vs n = 8; 5%, $P = 0.01$). The disease expression within families was very heterogeneous without characteristic familial patterns (data not shown).

MAJOR ADVERSE CARDIAC EVENTS AMONG HCM INDEX PATIENTS AND AFFECTED RELATIVES CARRYING P/LP VARIANTS. Sudden cardiac death. Twenty-six index patients (26/183; 14%) and 21 relatives (21/160; 13%) with HCM experienced SCD ($P = 0.80$) (Table 2).

This included deceased index patients (n = 4) and relatives (n = 11) who died suddenly as their initial disease manifestation and received a diagnosis of HCM following autopsy.

The remaining 10 deceased index patients and 8 relatives were followed for a median period of 6 years (IQR: 4-15 years) before they died without having received an ICD. Using the ESC risk calculator for SCD in HCM retrospectively, 3 of these patients had a risk score >6%, 4 between 4% and 6%, and 11 below 4% (data not shown).[1]

Six of the index patients and one relative were resuscitated successfully from a cardiac arrest as their initial disease manifestation, and additionally, 6 of the index patients and one relative received appropriate ICD therapy for ventricular arrhythmias.

Heart failure and disabling stroke. Four percent (8/183) of both index patients and affected relatives (7/160) died from endstage heart failure ($P = 0.9$) at a median age of 56 years (IQR: 45-68) (Supplemental Figure 2). Twenty-seven percent (50/183) of index patients and 15% (24/160) of affected relatives had atrial fibrillation, of whom all, except for 2 relatives, received anticoagulants including Warfarin (n = 7; 10%) and direct oral anticoagulants (DOACs) (n = 65; 90%). No disabling strokes were observed during follow-up (**Table 1**).

Number and incidence rate of MACE. There was no difference in the absolute number of MACE among index patients and affected relatives (19% [34/183] vs 18% [28/160], $P = 0.90$), nor in incidence rates of MACE during 8 years of follow-up (12 cases/1,000 person-years [95% CI: 8-18] vs 15 cases/1,000 person-years [95% CI: 9-25]); incidence rate ratio: 0.8 (95% CI: 0.4-1.7) ($P = 0.60$) (**Central Illustration**). Likewise, there were no differences in MACE between sexes (**Figure 3A**).

However, MACE hazard ratio for patients diagnosed before the age of 18 years was significantly higher compared to HCM patients diagnosed at older ages (HR: 4.7 (95% CI: 1.8-12.0), $P < 0.01$) (**Figure 3B**, Supplemental Tables 2 and 3). There were no significant differences in the hazard ratio of MACE when considering individual genes or variants ($P = 0.12$) (Supplemental Table 2).

Clinical characteristics of all HCM patients who experienced MACE. There were no differences in clinical characteristics between index patients and relatives who experienced MACE (**Table 2**). However, patients who experienced MACE were significantly younger at diagnosis than HCM patients without MACE (36 ± 16 years vs 46 ± 16 years; $P < 0.01$) (**Table 2**). In addition, they were characterized by having a family history of SCD more frequently (40% vs 20%; $P < 0.01$), having more episodes of nonsustained ventricular tachycardia (32% vs 17%; $P < 0.03$), and having more unexplained syncopes during the follow-up (24% vs 9%; $P < 0.01$).

Patients who experienced MACE were also more likely to have atrial fibrillation (38% vs 20%, $P < 0.01$). Finally, HCM patients with MACE had left ventricular

TABLE 2 Characteristics of HCM Patients Experiencing MACE

Comparison of HCM Patients With and Without MACE

	HCM Patients With MACE (n = 62)	HCM Patients Without MACE (n = 281)	*P* Value
Index patients	34 (55%)	149 (53%)	0.80
Age of diagnosis (y)	36 ± 16	46 ± 16	<0.01
Age of MACE (y)	43 ± 19	-	-
Male	33 (53.2%)	168 (59.8%)	0.34
History of family SCD	25 (40.3%)	56 (19.9%)	<0.01
NYHA functional class III-IV at diagnosis	2/46 (4.3%)	2/260 (1.2%)	0.11
History of unexplained syncope[a]	11/46 (23.9%)	23/260 (8.8%)	<0.01
Nonsustained VT on Holter[a]	13/41 (31.7%)	43/254 (16.9%)	0.03
Primary prophylactic ICD	13/62 (21.0%)	80/281 (28.5%)	0.22
Maximum LV wall thickness (mm)[a]	18 (15-23)	18 (15-21)	0.58
LVOT gradient >30 mm Hg[a]	1/47 (2.1%)	44/281 (15.7%)	0.01
Left atrial diameter (mm)	38 (38-41)	38 (35-40)	0.22
Atrial fibrillation during follow-up	18/47 (38%)	55/281 (20%)	<0.01
Age at onset of atrial fibrillation, y	54 (49-59)	56 (48-65)	0.39

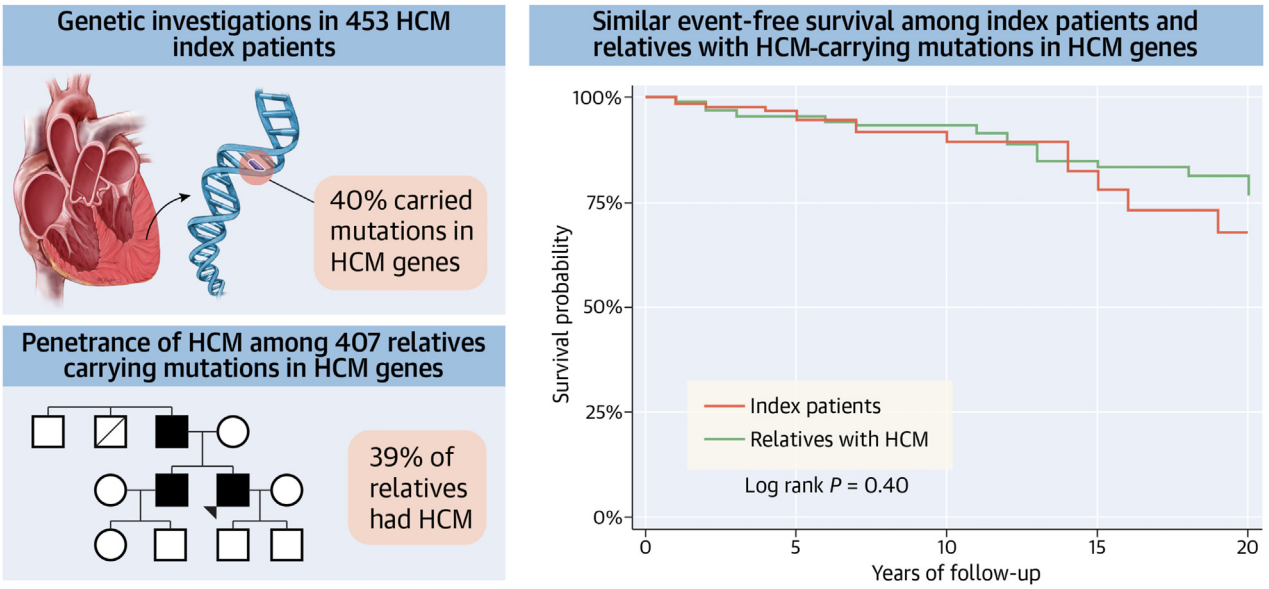
Comparison of MACE Among Index Patients and Affected Relatives

	Index Patients With MACE (n = 34)	Relatives With MACE (n = 28)	*P* Value
Age of diagnosis (y)	38 ± 16	34 ± 17	0.44.
Age of MACE (y)	45 ± 18	41 ± 20	0.33
Male	18 (52.9%)	15 (53.6%)	0.96
Cardiac symptoms at diagnosis	15/30 (50%)	7/17 (41.2%)	0.56
Nonsustained VT on Holter	9/30 (30.0%)	3/17 (17.6%)	0.35
Maximum LV wall thickness (mm)	20 (15-24)	16 (14-21)	0.19
LVOT gradient >30 mm Hg	-	1 (3.6%)	-
Left atrial diameter (mm)	40 (35; 45)	39.5 (35;43)	0.78
Atrial fibrillation during follow-up	11/30 (37%)	7/17 (41%)	0.76
Age at onset of atrial fibrillation, y	52 (41-56)	61 (55-67)	0.07
Type of MACE			
SCD/aborted SCD at diagnosis[b]	10 (29.4%)	12 (42.9%)	0.27
SCD/aborted SCD during follow-up	10 (29.4%)	8 (28.6%)	0.94
Appropriate shock from primary prevention ICD	6 (17.6%)	1 (3.6%)	0.08
Heart failure mortality/HTx	8 (23.5%)	7 (25.0%)	0.89
Disabling stroke	-	-	-

Values are n (%), mean ± SD, n/N (%), or median (IQR). [a]At baseline or during follow-up. [b]4 deceased relatives did not receive an autopsy but were assumed to have died from HCM since they were shown to be obligate carriers of the P/LP variant segregating with HCM in their family.

HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVOT = left ventricular outflow tract; MACE = major adverse cardiac event(s); SCD = sudden cardiac death; VT = ventricular tachycardia.

CENTRAL ILLUSTRATION **Disease Expression of HCM Is Similar in Index Patients and Relatives Carrying Mutations in HCM Genes**



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A total of 183 index patients and 407 of their relatives all carrying P/LP variants were investigated. The penetrance of HCM among relatives was 39%. The disease expression of HCM was similar in index patients and their affected relatives. HCM = hypertrophic cardiomyopathy; P/LP = pathogenic/likely pathogenic variants.

outflow tract obstruction less frequently than HCM patients without MACE (2% vs 16%; $P = 0.01$).

DISCUSSION

Previous studies have primarily focused on investigations of the disease expression in HCM among index patients who were diagnosed due to symptoms of cardiac disease. Only a few studies have performed clinical and genetic investigations of relatives and suggested that the disease expression among relatives was less severe.[5-7] However, these studies have not provided data to enable a direct comparison of the clinical characteristics among index patients and their relatives within the same cohort of affected families. Furthermore, no information about the percentage of relatives available for the investigations in relation to all relatives at risk of disease development has been available. This has made it difficult to establish the representativeness of these cohorts in a general referral setting.

The current investigation included 90% of all genotype-positive HCM index patients (n = 183) referred for evaluation at dedicated clinics for hereditary cardiac conditions and 84% of their first-degree relatives (n = 407) who also carried P/LP variants and were alive at the time of the study. This made a unique cohort of almost all relatives who underwent thorough clinical and genetic investigations. Furthermore, the participants in the study underwent follow-up for an average period of 7 years. Therefore, the results were most likely to represent the disease expression of HCM in a referral setting.

The overall penetrance of the condition among relatives was 39%. Relatives had an average age of 42 years at disease onset with the highest penetrance rates among carriers above 50 years of age, which resembled results from previous reports (**Figure 2B**).[7,17] Since the penetrance reflected the actual age distribution among all variant carriers, including healthy relatives, who had an average age of only 37 years, it is likely that more individuals will become affected with increasing age.[18] These findings support current guideline recommendations for long-term clinical follow-up of healthy carriers.[1,17,19,20]

DISEASE EXPRESSION AND MACE. Index patients had a significantly higher burden of cardiac symptoms than affected relatives at the time of diagnosis,

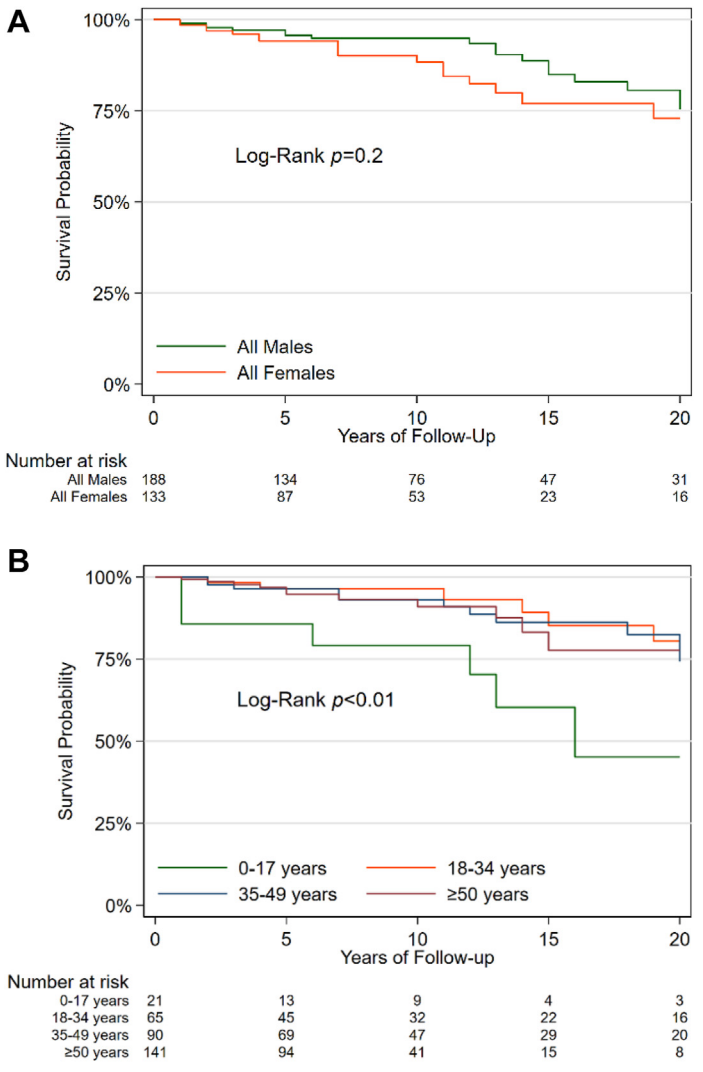
which may reflect that index patients had a more pronounced disease expression, including a higher degree of both LV hypertrophy and LV outflow obstruction (**Table 1**). These findings were likely to be explained by the fact that relatives had been diagnosed due to family screening at an earlier stage of disease development, unlike index patients, who were referred primarily due to symptoms of cardiac disease.

The disease expression among index patients and relatives who experienced MACE was similar with a comparable risk profile for SCD (**Table 2B**). The annual rate of MACE was 1.3% and resembled previously reported cardiac mortality rates for index patients of 1 to 2%.[1] Early-onset of HCM was associated with a particularly bad outcome in patients who were characterized by having few symptoms despite the presence of pronounced LV hypertrophy (Supplemental Table 3). These findings highlighted the importance of family screening for presymptomatic identification of HCM patients at high risk of MACE. Surprisingly, patients with MACE had less left ventricular outflow tract obstruction than other HCM patients, which was not readily explained and may have been an accidental finding due to the relatively low number of events.

CLINICAL IMPLICATIONS. The results of the current study suggested that affected relatives and index patients had a similar disease expression with a comparable risk profile for MACE and long-term prognosis. Furthermore, the results indicated that family screening and regular risk assessment for SCD by use of the ESC risk calculator resulted in appropriate ICD therapy in 9% (6/69) of index patients and 4% (1/25) of relatives who received a primary prophylactic ICD. Some HCM patients in the current study experienced SCD before the implementation of the ESC model for risk assessment and, therefore, had not received a primary prophylactic ICD.[1] Although hypothetical, assuming that the model had been used for risk assessment in the entire study period, it may have been possible that an additional 39% (7/18) of the SCDs would have been prevented if these patients had received a primary prophylactic ICD and appropriate therapies.

Surprisingly, no patients experienced stroke episodes or major bleedings, although 15% of affected relatives and 27% of index patients were in atrial fibrillation and received treatment with Warfarin (10%) or DOAC (90%). This suggested that the regular use of Holter recordings during follow-up to identify atrial fibrillation was valuable and that treatment with either Warfarin or DOAC was evenly efficient.

FIGURE 3 Event-Free Survival of HCM Index Patients and Affected Relatives



(A) No difference in event-free survival was observed between male and female patients with HCM. (B) A diagnosis of HCM before the age of 18 years was associated with a significantly higher MACE hazard ratio compared to HCM patients diagnosed at older ages (HR: 4.7 [95% CI: 1.8-12.0], $P < 0.01$). HCM = hypertrophic cardiomyopathy.

In contrast to previous investigations, which suggested that the disease expression among relatives was less severe compared to index patients, the current results showed that genotype-positive HCM index patients and their affected relatives had a similar disease expression with the same risk of adverse events and SCD. This finding was likely to be explained by the fact that significantly more genotype-positive relatives per index patient participated in the current investigation compared to

previous studies. Thereby, it was likely that the present results were associated with a more comprehensive and accurate description of the actual disease expression among relatives (2.2 vs 1.7, $P = 0.02$).[5-7]

Based on the current findings, it appears that the cost-benefit of family screening programs and repeated risk profiling for SCD are indeed appropriate and justifiable.

STUDY LIMITATIONS. The study was conducted at 5 tertiary referral hospitals, including one transplant center, which may have introduced referral bias towards more severely affected HCM families and thereby overestimated MACE. In addition, healthy carriers were generally younger than affected relatives, which was likely to underestimate the age-dependent penetrance. Finally, 16% of relatives declined to participate in the study, which may have introduced selection bias towards more symptomatic relatives.

CONCLUSIONS

The disease expression of HCM was similar among genotype-positive index patients and their affected relatives, including a comparable risk profile for SCD. The penetrance among relatives was 39%, with a particularly bad outcome in patients with early disease onset. The results strongly support the provision of family screening programs and regular follow-up of relatives at risk of disease development. Thereby, it may be possible to improve management and diminish the risk of severe disease complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The rate of major cardiac events was similar in genotype-positive index patients with HCM and their affected relatives.

TRANSLATIONAL OUTLOOK: Unaffected relatives who carry P/LP variants in HCM genes have no risk of MACE. Future studies should investigate mechanisms associated with the onset of HCM to optimize management of relatives at risk of disease development.

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KEY WORDS cardiomyopathy, follow-up studies, genetic counseling, genotype, hypertrophic, penetrance

APPENDIX For supplemental tables and figures, please see the online version of this paper.