



Sudden Cardiac Death-Relevant Events of Hypertrophic Cardiomyopathy in a Regional Japanese Cohort

— Results From the Kochi RYOMA Study —

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Background: Sudden cardiac death (SCD) is a most devastating complication of hypertrophic cardiomyopathy (HCM). The aim of this study was to clarify the clinical features of HCM in patients who experienced SCD-relevant events in an aged Japanese community.

Methods and Results: In 2004, we established a cardiomyopathy registration network in Kochi Prefecture, and herein report on 293 patients with HCM who are followed as part of the registry. The mean (\pm SD) age at registration and diagnosis was 63 ± 14 and 56 ± 16 years, respectively. SCD-relevant events occurred in 19 patients during a mean follow-up period of 6.1 ± 3.2 years (incidence rate 1.0%/year): sudden death in 9 patients, successful recovery from cardiopulmonary arrest in 4 patients, and appropriate implantable cardioverter–defibrillator discharge in 6 patients. At registration, 13 patients were in the dilated phase of HCM (D-HCM). During the follow-up period, HCM developed to D-HCM in 21 patients; thus, 34 patients in total had D-HCM. Multivariate analysis revealed that D-HCM at registration or during follow-up and detection of non-sustained ventricular tachycardia (NSVT) during follow-up were significant predictors of SCD-relevant events.

Conclusions: In this HCM population in an aged Japanese community, the annual rate of SCD-relevant events was 1.0%. HCM developed to D-HCM in a considerable number of patients, and D-HCM and NSVT were shown to be independently associated with an increased risk of SCD-relevant events.

Key Words: Arrhythmia; Dilated phase; Hypertrophic cardiomyopathy; Sudden cardiac death

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features.^{1–5} Sudden cardiac death (SCD) is the most devastating complication of HCM. Although several predictors of SCD have been reported,^{6–8} there have been few studies on the risk factors for SCD in Japanese community-based HCM cohorts. In 2004 we established the Kochi Cardiomyopathy Network, the named Kochi RYOMA (Registry of Myocardial Diseases) Study, to provide detailed information on the clinical features of HCM in a prospectively assembled

regional patient cohort in an aged Japanese community.⁹ We recently reported the patients' characteristics and clinical course of HCM in this unselected cohort.¹⁰ In the present study, we assessed the clinical features of HCM in patients who experienced SCD-relevant events.

Methods

Subjects

In 2004 we established the Kochi Cardiomyopathy Network, which consists of 9 hospitals serving as primary, secondary,

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Table 1. Clinical Characteristics of the 293 Patients With HCM at Registration	
Age at registration (years)	63±14
Male sex	197 (67)
Age at diagnosis (years)	56±16
Age at diagnosis <40 years	40 (14)
Reason for diagnosis: symptoms	136 (46)
Family history of HCM	76 (26)
Family history of SCD	52 (18)
Presence of symptoms at registration	185 (63)
NYHA functional class	
Class I	163 (56)
Class II	109 (37)
Class III	21 (7)
Class IV	0 (0)
Syncope	12 (4)
Presence of AF at registration	86 (29)
ICD implantation	4 (1)
PM implantation	13 (4)
Presence of NSVT ^A	60 (28)
ECG data at registration	
Subtype	
HOCM	40 (14)
MVO	8 (3)
D-HCM	13 (4)
Apical HCM	52 (18)
Others	180 (61)
Presence of LVOT obstruction	36 (12)
Maximum LVWT (mm)	19.0±3.9
LVEDD (mm)	46.3±6.0
FS (%)	40.9±8.5
Left atrial diameter (mm)	44.3±7.5
Medications at registration	
β-blocker	119 (41)
Calcium antagonist	79 (27)
ACEI or ARB	78 (27)
Diuretics	50 (17)
Antiarrhythmic drugs	64 (22)
Anticoagulation therapy	79 (27)

Data are presented as the mean±SD or n (%). ^AHolter echocardiography (ECG) was performed in 213 patients during the follow-up period. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; D-HCM, dilated phase of HCM; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, LV end-diastolic pressure; LVOT, LV outflow tract; LVWT, LV wall thickness; MVO, midventricular obstruction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PM, pacemaker; SCD, sudden cardiac death.

and tertiary referral medical centers for cardiovascular patients in Kochi Prefecture, Japan, home to approximately 800,000 inhabitants. Between February 2004 and December 2013, 305 patients with a diagnosis of HCM were registered in the Kochi Cardiomyopathy Network. The diagnosis of HCM was based on echocardiographic demonstration of unexplained left ventricular hypertrophy (LVH; i.e., maximum left ventricular [LV] wall thickness ≥15 mm). Shortly after a diagnosis of HCM was made, 3 patients were diagnosed as having specific cardiomyopathy (1 patient with

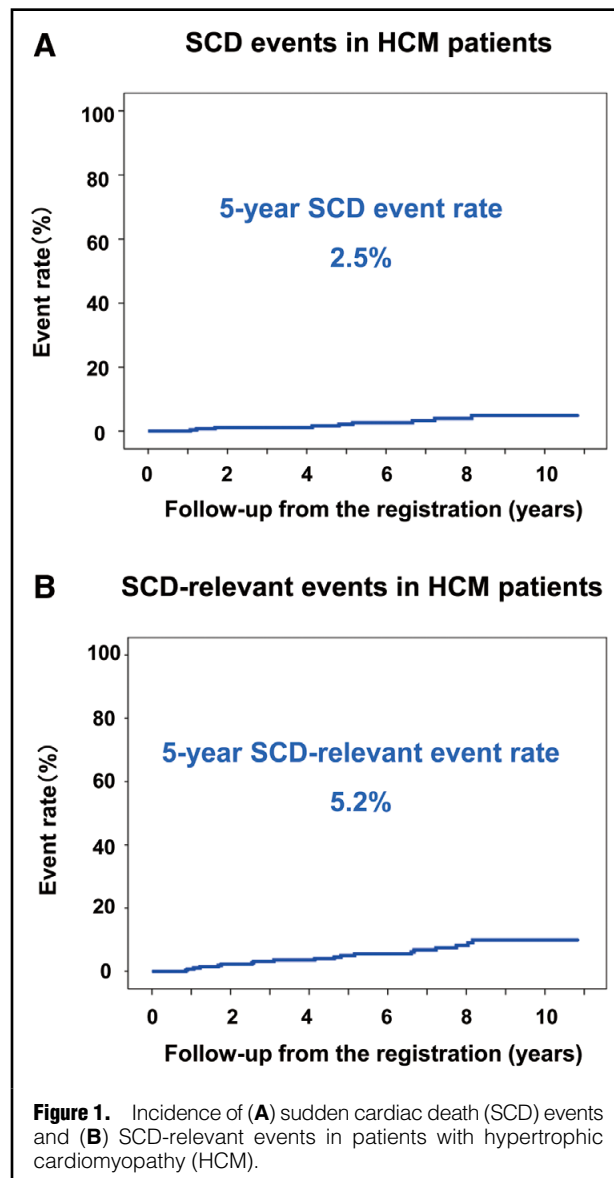


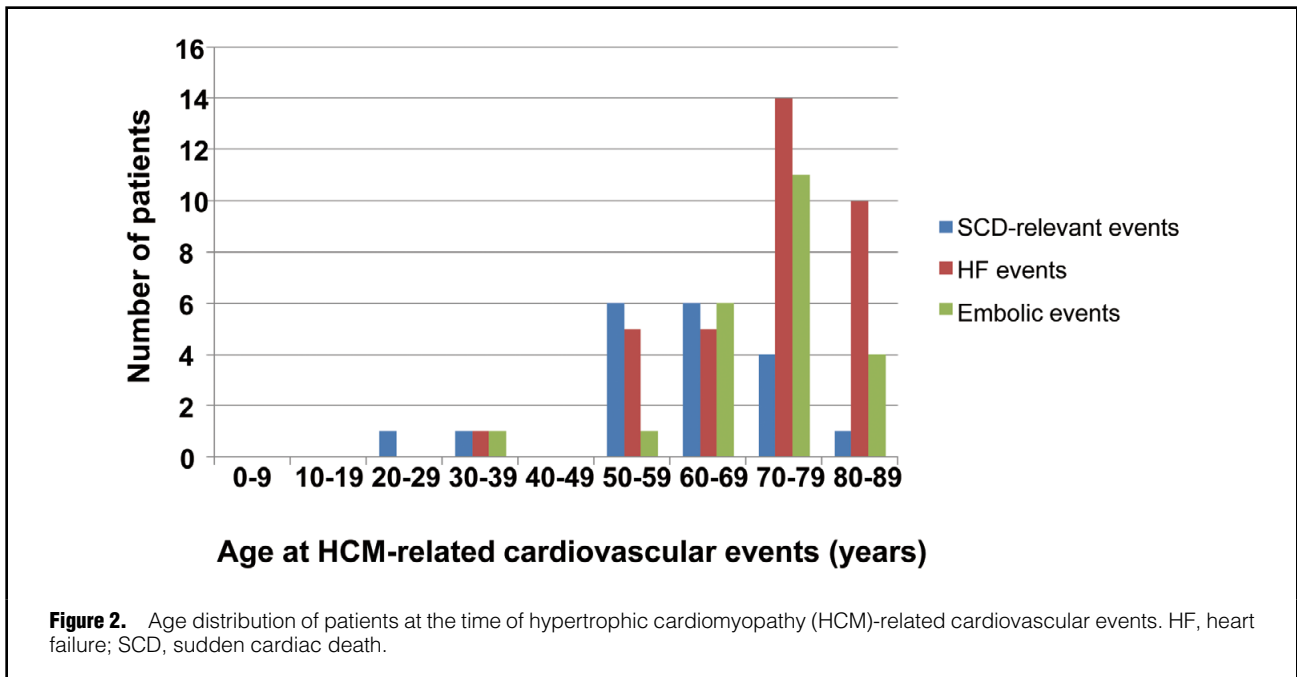
Figure 1. Incidence of (A) sudden cardiac death (SCD) events and (B) SCD-relevant events in patients with hypertrophic cardiomyopathy (HCM).

cardiac amyloidosis and 2 patients with cardiac involvement of Fabry disease) and excluded from this study, leaving 302 registered patients. In this longitudinal study, further 9 patients with no follow-up data were excluded; thus, the final study population consisted of 293 patients.

This study was approved by the Ethics Committee on Medical Research of Kochi Medical School, and followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation at each participating institution. Informed consent was obtained from all patients or their parents, in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Clinical Evaluation

Patient evaluation included a medical history, clinical examination, 12-lead electrocardiography (ECG), M-mode, 2-dimensional (2D), and Doppler echocardiography, and ambulatory 24-h Holter ECG analysis. The severity and distribution of LVH were assessed in the parasternal short-



axis plane at the level of the mitral valve and papillary muscle. LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured from M-mode and 2D images obtained from parasternal long-axis views, and fractional shortening (FS) was calculated as follows:

$$FS = (LVEDD - LVESD) / LVEDD \times 100$$

The LV outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation. Non-sustained ventricular tachycardia (NSVT) was defined as ≥ 3 consecutive ventricular beats at a rate of ≥ 120 beats/min, lasting for < 30 s.

Based on morphologic and hemodynamic assessments by echocardiography, patients were divided into the following 5 groups: (1) hypertrophic obstructive cardiomyopathy (HOCM), defined as the presence of basal LV outflow tract (LVOT) obstruction (gradient ≥ 30 mmHg at rest); (2) midventricular obstruction (MVO), defined as the presence of systolic LV cavity obliteration at the midventricle creating MVO with a peak systolic gradient ≥ 30 mmHg at rest; (3) dilated phase of HCM (D-HCM), defined as LV systolic dysfunction of global ejection fraction (EF) $< 50\%$ (global EF was determined using the modified Simpson's method); (4) apical HCM, defined as hypertrophy confined to the LV apex; and (5) others, which included HCM without obstruction other than D-HCM and apical HCM.¹¹

For prognostic analysis, 3 modes of HCM-related adverse cardiovascular events were defined as follows: (1) SCD-relevant events were defined as a composite of sudden death, in which unexpected sudden collapse occurred in patients who had previously experienced a relatively stable or uneventful clinical course, successful recovery from ventricular fibrillation or spontaneous sustained ventricular tachycardia associated with hemodynamic instability, and appropriate implantable cardioverter-defibrillator (ICD) discharge; (2) composite heart failure (HF) events included HF-related death and hospitalization for HF; and (3) thromboembolic events were the composite of embolic

stroke-related death and admission for arterial thromboembolic events. Data on survival and the clinical status of patients were obtained during serial clinic visits or from records on the patients' clinical charts, including information from other institutes. The study closed on December 31, 2014.

Data Analysis

All data are expressed as mean \pm SD or frequency (percentage). The significance of differences in continuous variables was assessed using Student's t-test or the Mann-Whitney's U-test. Pearson's Chi-squared test was used for comparisons between non-continuous variables, and Fisher's exact test was used when the expected frequency was < 5 . Event-free estimate curves were calculated by the Kaplan-Meier method, and the log-rank test was used for comparison. The multivariate Cox proportional hazards model was used to analyze the relationships between SCD-relevant events and prognostic parameters including some variables with $P \leq 0.05$ in univariate analysis and conventional risk factors for SCD. Statistical significance was defined as 2-sided $P \leq 0.05$. Statistical analyses were performed using SPSS version 14.0J (SPSS Inc., Chicago, IL, USA).

Results

Clinical Characteristics at Registration

The clinical characteristics of the 293 patients with HCM at registration are summarized in **Table 1**. Mean patient age at registration and diagnosis was 63 ± 14 (range 7–88) and 56 ± 16 (range 6–87) years, respectively; 197 patients (67%) were men. Forty patients (14%) were diagnosed with HCM at < 40 years of age. Seventy-six patients (26%) had proven familial HCM and 52 patients (18%) had a family history of sudden death. Most of the 293 patients were asymptomatic or mildly symptomatic at registration: 163 (56%) were New York Heart Association (NYHA) Class I, 109 (37%) were NYHA Class II, and only 21 (7%) were

	SCD-relevant events		P-value
	Yes (n=19)	No (n=274)	
Age at registration (years)	57±15	64±14	0.066
Male sex	11 (58)	186 (68)	0.370
Age at diagnosis (years)	49±17	57±13	0.044
Reason for diagnosis: symptoms	10 (53)	126 (46)	0.574
Family history of HCM	10 (53)	66 (24)	0.012
Family history of SCD	6 (32)	46 (17)	0.119
Presence of symptoms at registration	15 (79)	170 (62)	0.140
NYHA Class III	3 (16)	18 (7)	0.146
Syncope	2 (11)	10 (4)	0.178
Presence of AF at registration	9 (47)	77 (28)	0.075
Presence of NSVT ^A	12 (63)	48 (18)	<0.001
ECG data at registration			
Subtype			0.002
HOCM	3 (16)	37 (14)	
MVO	0 (0)	8 (3)	
D-HCM	4 (21)	9 (3)	
Apical HCM	0 (0)	52 (19)	
Others	12 (63)	168 (61)	
LVOT obstruction	3 (16)	33 (12)	0.716
Maximum LVWT (mm)	19.7±3.0	19.0±4.0	0.414
LVEDD (mm)	49.5±6.3	46.1±6.0	0.019
FS (%)	35.4±10.3	41.3±8.2	0.003
Left atrial diameter (mm)	49.6±8.6	43.9±7.3	0.002
D-HCM at final follow-up	10 (52)	24 (9)	<0.001
Medications at registration			
β-blocker	10 (53)	109 (40)	0.270
Calcium antagonist	3 (16)	76 (28)	0.256
ACEI or ARB	7 (37)	71 (26)	0.297
Diuretic	8 (42)	42 (15)	0.007
Antiarrhythmic drugs	8 (42)	56 (20)	0.041
Class Ia	5 (26)	36 (13)	0.160
Class Ib	0 (0)	6 (2)	1.000
Class Ic	0 (0)	5 (2)	1.000
Class III	3 (16)	8 (3)	0.027
Class IV	0 (0)	1 (1)	1.000
Anticoagulation therapy	9 (47)	70 (26)	0.038

Data are presented as the mean±SD or n (%). ^AHolter ECG was performed in 213 patients during the follow-up period. Abbreviations as in Table 1.

NYHA Class III. At registration, 86 patients (29%) had documentation of atrial fibrillation (AF). Of all 293 patients, 40 were in the HOCM group, 8 were in the MVO group, 13 were in the D-HCM group, 52 were in the apical HCM group, and 180 were in the “other” group.

SCD-Relevant Events

The mean follow-up period from registration of the patient cohort was 6.1±3.2 years, and 44 patients died. Of these 44 patients, HCM-related deaths occurred in 23: SCD in 9 patients, HF deaths in 11 patients, and embolic stroke deaths in 3 patients. In the 9 patients with SCD, unexpected death occurred during physical labor in only 1 patient. The remaining 8 patients died in a situation of no physical stress (8 patients while sleeping, 2 patients while relaxing after dinner). **Figure 1A** shows the incidence of SCD events. The 5-year SCD rate was 2.5% and the annual SCD

mortality rate was 0.5%.

With regard to HCM-related adverse events, a total of 77 cardiovascular events occurred in 70 patients during the follow-up period. SCD-relevant events occurred in 19 patients, including sudden death in 9 patients, successful recovery from cardiopulmonary arrest in 4 patients, and appropriate ICD discharge in 6 patients; HF events occurred in 35 patients, including 11 HF deaths; and thromboembolic events occurred in 23 patients, including 3 embolic stroke deaths. The distribution of ages at the time of HCM-related adverse events is shown in **Figure 2**. Patients in whom SCD-relevant events occurred were younger than patients with HF or embolic events. **Figure 1B** shows the incidence of SCD-relevant events. The 5-year SCD-relevant event rate was 5.2% and the rate of SCD-relevant events was 1.0% per year. **Table 2** lists the clinical characteristics at registration of patients with and without

Table 3. Predictors of SCD-Relevant Events (Multivariate Cox Proportional Hazards Model)		
	Hazard ratio	P-value
Model 1		
Age at diagnosis	1.006	0.708
Male sex	0.580	0.300
Family history of HCM	1.422	0.555
Family history of SCD	1.418	0.544
Presence of syncope	1.674	0.651
NSVT	3.092	0.056
Maximum LVWT	1.039	0.558
Left atrial diameter	1.029	0.424
LVOT obstruction at registration	2.768	0.189
D-HCM at registration or follow-up	5.008	0.028
Model 2		
Family history of SCD	1.833	0.234
Presence of syncope	1.134	0.908
NSVT	3.290	0.029
Maximum LVWT	1.030	0.587
LVOT obstruction at registration	3.394	0.102
D-HCM at registration or follow-up	6.482	0.001

Abbreviations as in Table 1.

SCD-relevant events. There was no sex difference between the 2 groups. The prevalence of a family history of HCM and detection of NSVT in patients with SCD-relevant events were significantly higher in patients with than without SCD-relevant events. Echocardiography showed that the prevalence of HOCM was comparable between the 2 groups. Patients in the SCD-relevant event group had a higher prevalence of D-HCM and a lower prevalence of apical HCM. Patients with SCD-relevant events had a larger LVEDD and left atrial size and lower LV FS than did patients without SCD-relevant events.

Regarding the prevalence of D-HCM, 13 patients were in D-HCM at registration. During the follow-up period, development of HCM to D-HCM occurred in an additional 21 patients, with the annual incidence of D-HCM being 1.2%; thus, in all, 34 patients had D-HCM. Of these 34 patients, 10 experienced an SCD-relevant event. Of particular note is that 7 of these 10 patients had lethal arrhythmic events as the first HCM-related events without a prior HF event.

Predictors of SCD-Relevant Events

Multivariate Cox proportional hazards models are shown in Table 3. Model 1 included parameters that were statistically significant according to univariate analysis (age at diagnosis, sex, family history of HCM, left atrial diameter, D-HCM) and conventional risk factors (family history of SCD, syncope, presence of NSVT, maximum LV wall thickness, presence of LVOT obstruction); Model 2 included only the conventional risk factors for SCD and D-HCM. Detection of NSVT and progression to D-HCM at registration or during follow-up were significant predictors of SCD-relevant events in our regional Japanese HCM cohort.

Figure 3A shows SCD-relevant events in HCM patients with and without NSVT. For SCD-relevant events, NSVT on Holter ECG had negative and positive predictive values of 97% and 20%, respectively, and sensitivity and specificity of 63% and 82%, respectively. Figure 3B shows SCD-

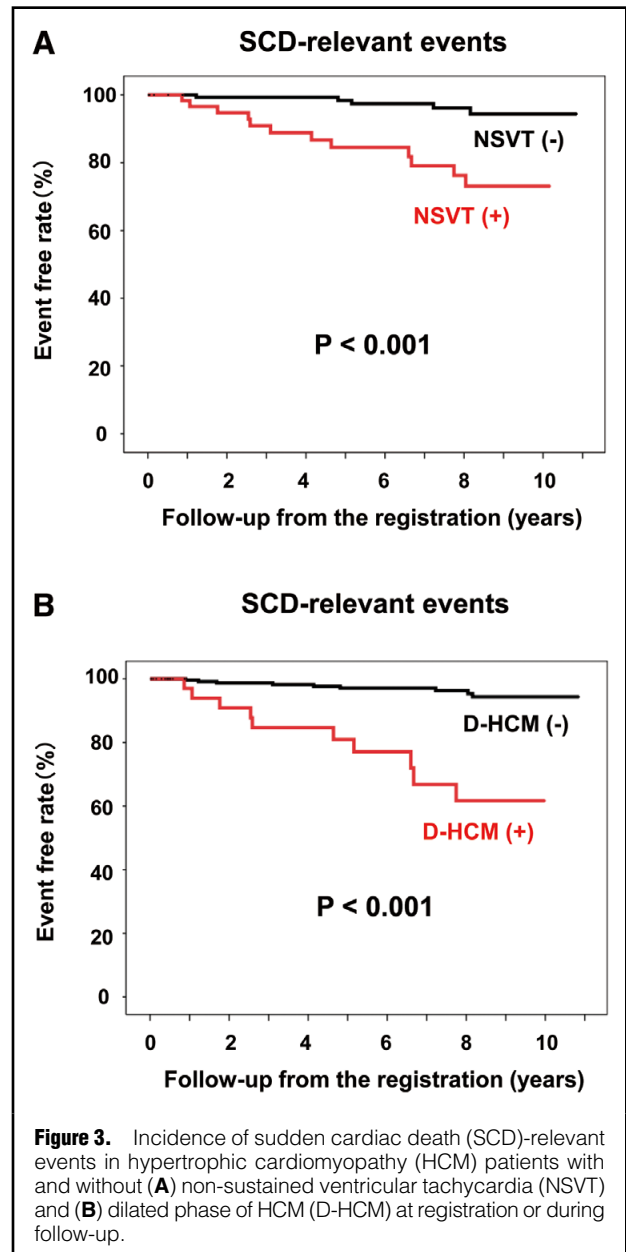


Figure 3. Incidence of sudden cardiac death (SCD)-relevant events in hypertrophic cardiomyopathy (HCM) patients with and without (A) non-sustained ventricular tachycardia (NSVT) and (B) dilated phase of HCM (D-HCM) at registration or during follow-up.

relevant events in HCM patients with and without the progression of HCM to D-HCM. Of 19 patients with SCD-relevant events, 10 (53%) had D-HCM. D-HCM had negative and positive predictive values of 97% and 29%, respectively, and sensitivity and specificity of 53% and 91%, respectively, for predicting SCD-relevant events. In the remaining 9 patients without D-HCM, 7 had one or more conventional SCD risk factor, and the remaining 2 patients had no conventional risk factors (they had only paroxysmal AF).

Discussion

HCM is a primary myocardial disorder with a heterogeneous clinical presentation and course.¹⁻⁵ The natural history of HCM varies from an asymptomatic and benign clinical course to sudden premature death and advanced

HF. To the best of our knowledge, the present study is the first prospective multicenter investigation showing the clinical profile of SCD-relevant events in a regional Japanese HCM population.

Regional HCM Cohort and SCD-Relevant Events

Our regional cohort in the Kochi RYOMA study was older than HCM cohorts in previous studies.²⁻⁵ This age distribution of patients in the present study is probably due to the fact that Kochi Prefecture, where this study was performed, is located far from urban areas and is one of the most aged communities in Japan. We think that, at least in Japanese rural regions, many patients with this disease are middle-aged or elderly despite the fact that HCM is regarded as a genetic disorder. Recently, we reported that the survival rate in this cohort was favorable with an HCM-related annual mortality rate of 1.3%.¹⁰ In the present study, we focused on SCD-relevant events and found that the annual mortality rate of SCD was 0.5% and that the rate of SCD-relevant events was 1.0% per year; these findings are in accordance with previously reported data obtained from community-based cohorts for HCM in Western countries.^{4,5} Although SCD-relevant events have been considered to be closely associated with young age in HCM patients, most of the patients (89%) in the present HCM population experienced SCD-relevant events after 50 years of age.

Predictors of SCD-Relevant Events

Regarding risk factors for overall HCM-related adverse events in this HCM population, we have already reported that NYHA Class III, the presence of AF, LVOT obstruction, and lower LV FS at registration are significant predictors.¹⁰ In the present study, multivariate analysis revealed that the presence of NSVT and D-HCM (at registration or during follow-up) were significant predictors of SCD-relevant events. These 2 factors are known to be associated with SCD.¹²⁻¹⁹ First, NSVT is one of the major risk factors for SCD in addition to syncope, a family history of SCD, and severe cardiac hypertrophy, because several guidelines for the diagnosis and treatment of HCM show the importance of NSVT in risk stratification for SCD, including the 2011 American College of Cardiology Foundation/The American Heart Association (ACCF/AHA) guidelines, the 2014 European Society of Cardiology (ESC) guidelines, and the 2018 Japanese Circulation Society (JCS) guidelines.^{7,8,20} Previous studies showed that the proportion of patients with NSVT increased with age, and up to 20–30% of patients in HCM cohorts may have NSVT.^{12,13} In the present patient population, NSVT was identified by Holter ECG in at least 28% of patients. Although Monserrat et al reported that NSVT was associated with a substantial increase in SCD risk in young patients with HCM,¹³ the presence of NSVT was also an independent predictor of SCD-relevant events in our aged HCM population. NSVT was previously reported to have a low positive predictive value and a relatively high negative predictive value for SCD in patients with HCM.¹⁴ Similarly, in the present study, NSVT detected by Holter ECG had a 20% positive predictive value and a 97% negative predictive value. Therefore, although high-risk HCM patients cannot always be identified by the presence of NSVT, confirmation of the absence of NSVT using Holter ECG monitoring is considered useful for identifying patients at low risk of SCD.

Second, it is well known that HCM in a subset of

patients progresses to the ‘dilated’ or ‘end-stage’ phase characterized by LV systolic dysfunction and that patients with D-HCM have a poor prognosis.^{16-19,21} In patients with D-HCM, the poor clinical course is due not only to refractory HF, but also SCD. Regarding the severity of cardiac fibrosis evaluated by late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging, D-HCM is typically associated with extensive LGE (25–50% of the whole LV), and more severe fibrosis is related to a greater risk of lethal arrhythmic events.²² Kawarai et al reported that patients with D-HCM had a high incidence of SCD-relevant events: SCD occurred in 47% of patients over a mean follow-up period of 5±3 years after progression to D-HCM.¹⁷ In the present HCM population, 10 of 34 D-HCM patients experienced SCD-relevant events. Furthermore, it is notable that 7 of these 10 patients had a lethal arrhythmic event as the first HCM-related event without a prior HF event. Considering the frequent SCD events preceding refractory HF status in D-HCM patients, early intervention with ICD implantation should be considered for these patients. However, the high risk of SCD in D-HCM patients has not been directly reflected in the 2011 ACCF/AHA and 2014 ESC guidelines for HCM management.^{7,8} Nakagawa et al reported that the recommendation for ICD implantation by the 2003 ACC/ESC, 2011 ACCF/AHA, and 2014 ESC guidelines was not based on appropriate SCD risk stratification in D-HCM patients.²³ According to the latest 2018 JCS guidelines published, D-HCM itself is regarded as an important SCD risk modifier.²⁰ We would like to emphasize the clinical effect of D-HCM concerning SCD-relevant events in HCM.

Study Limitations

This study has several limitations that need to be acknowledged. First, the number of SCD-relevant events was small. Therefore, some of the statistical analyses may have been affected, and we may have missed other independent markers for stratification of SCD risk in patients with HCM. Second, Holter monitoring should have been performed in all patients at registration. Only approximately 70% of patients had Holter ECG monitoring during the follow-up period. There may be measurement bias in diagnosis of NSVT. Holter ECG may not have been performed uniformly, but rather in patients with severe symptoms, such as syncope. Third, CMR imaging data were not included in this study. Several studies demonstrated that extensive LGE in CMR was associated with the risk of SCD events in HCM.^{24,25} Therefore, further studies on prognostic factors for SCD in patients with HCM are needed. In 2015, we established a large-scale registration survey of patients with HCM throughout Japan, named the J-HCM Registry Study. This prospective registration study is ongoing, and we believe that this multicenter project will provide important information on prognostic factors in HCM patients, particularly for SCD.

Conclusions

In the unselected Kochi RYOMA registry in an aged Japanese community, the annual rate of SCD-relevant events was 1.0%. In this HCM population, HCM developed to the dilated phase in a considerable number of patients, and D-HCM and NSVT were shown to be independently associated with an increased risk of SCD-relevant events.

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IRB Information

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