ORIGINAL RESEARCH

Prognostic Implication of First-Degree Atrioventricular Block in Patients With Hypertrophic Cardiomyopathy

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Background—The association between first-degree atrioventricular block (AVB) and life-threatening cardiac events in patients with hypertrophic cardiomyopathy (HCM) remains unclear. This study sought to investigate whether presence of first-degree AVB was associated with HCM-related death in patients with HCM.

Methods and Results—We included 414 patients with HCM (mean age, 51±16 years; 64.5% men). The P-R interval was measured at the time of the initial evaluation and patients were classified into those with and without first-degree AVB, which was defined as a P-R interval ≥200 ms. HCM-related death was defined as a combined end point of sudden death or potentially lethal arrhythmic events, heart failure–related death, and stroke-related death. First-degree AVB was noted in 96 patients (23.2%) at time of enrollment. Over a median (interquartile range) follow-up period of 8.8 (4.9–12.9) years, a total of 56 patients (13.5%) experienced HCM-related deaths, including 47 (11.4%) with a combined end point of sudden death or potentially lethal arrhythmic events. In a multivariable analysis that included first-degree AVB and risk factors for life-threatening events, first-degree AVB was independently associated with an HCM-related death (adjusted hazard ratio, 2.41; 95% CI, 1.27–4.58; *P*=0.007), and this trend also persisted for the combined end point of sudden death or potentially lethal arrhythmic events (adjusted hazard ratio, 2.60; 95% CI, 1.28–5.27; *P*=0.008).

Conclusions—In this cohort of patients with HCM, first-degree AVB may be associated with HCM-related death, including the combined end point of sudden death or potentially lethal arrhythmic events. **(*J Am Heart Assoc*. 2020;9:e015064. DOI: 10.1161/JAHA.119.015064.)**

Key Words: first-degree atrioventricular block • hypertrophic cardiomyopathy • risk stratification • sudden cardiac death

The clinical course of hypertrophic cardiomyopathy (HCM) is highly variable, ranging from an asymptomatic status with a normal life expectancy to severely limiting dyspnea, embolic events, and sudden cardiac death (SCD).[1–6] Predicting life-threatening events in this population remains a challenge, given that established clinical markers that can help to stratify the risk of life-threatening events and make management decisions are still limited.

Prolongation of the P-R interval, conventionally known as first-degree atrioventricular block (AVB), had been recognized as a benign finding with no prognostic significance for cardiovascular events.[7,8] However, many recent studies have begun to report that this atrioventricular conduction disturbance is an important sign of future cardiac adverse outcomes, such as new-onset atrial fibrillation (AF), a heart failure hospitalization, and mortality, in various populations.[9–17] Nevertheless, the significance of first-degree AVB on adverse cardiac events in the HCM population remains unclear. Therefore, in the present study, we evaluated the prognostic significance of first-degree AVB on life-threatening events in a relatively large longitudinal cohort of patients with HCM.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. This study was conducted according to the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our hospital; need for informed consent was waived.

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Received November 10, 2019; accepted January 7, 2020.

Clinical Perspective

What Is New?

- In patients with hypertrophic cardiomyopathy, patients with first-degree atrioventricular block (AVB) had a higher probability of a future hypertrophic cardiomyopathy–related death as compared with those without first-degree AVB (adjusted hazard ratio of 2.41).
- Furthermore, patients with first-degree AVB had a higher probability of future sudden death or a potentially lethal arrhythmic event as compared with those without first-degree AVB (adjusted hazard ratio of 2.60).

What Are the Clinical Implications?

- It may be useful for clinicians to be vigilant for future life-threatening cardiac events in patients with hypertrophic cardiomyopathy when first-degree AVB is found on their ECGs.

Study Population

The study population included 507 consecutive patients clinically diagnosed with HCM at Tokyo Women's Medical University Hospital, Tokyo, Japan, from January 1, 2003 to December 31, 2016. The initial evaluation was the first clinical assessment, during which patients were echocardiographically diagnosed with HCM at our hospital, and the most recent evaluation was performed in the outpatient clinic up to December 31, 2017. HCM was diagnosed on the basis of the echocardiographic evidence of a hypertrophied nondilated left ventricle in the absence of any other cardiac or systemic disease capable of producing a similar degree of hypertrophy.[1,2] Other clinical parameters were recorded, including medication use, New York Heart Association functional class, results of ambulatory ECGs covering at least a 24-hour period, heart rate and rhythm, presence or absence of nonsustained ventricular tachycardia (minimum of 3 consecutive ventricular extrasystoles at a rate of ≥120 beats/min and lasting for <30 seconds), a family history of SCD, and a patient history of unexplained syncope. Implantable cardioverter defibrillators (ICDs) were implanted according to the customary practice during the follow-up, and the criteria for detection and treatment of ventricular arrhythmias were programmed at the discretion of the implanting electrophysiologists.

Definition of First-Degree AVB

Each patient underwent standard 12-lead ECGs (25 mm/s, 10 mm/mV) at the time of the initial evaluation. P-R intervals were measured in lead II or other limb leads, if necessary. P-R interval was defined as the interval from onset of the P wave (junction between the T-P isoelectric line and the beginning of the P-wave deflection) to the end of the P-R segment (junction with the QRS complex).[7,9,10] The P-R interval was initially transcribed from the computer interpretation of the ECG. Then, the experienced cardiologists, who were blinded to the combined end points, evaluated all the results to check whether or not there were discrepancies. In the cases with discrepancies, P-R intervals were measured manually by using digital calipers and the corrected P-R intervals were determined. First-degree AVB was defined as a P-R interval of ≥200 ms.[7]

Of the 507 patients with HCM, 93 were excluded from the present study according to the following reasons: 42 were in an AF rhythm at the time of the examination, 33 had ventricular pacing rhythms, 8 had no available ECGs for measuring P-R interval, and 10 were lost during follow-up. After these exclusions, 414 patients remained eligible for the present study (Figure 1).

Echocardiography

All patients underwent transthoracic echocardiography using commercially available ultrasound equipment. The left atrial dimension (LAD), measured from the parasternal long-axis view, was defined as the anteroposterior linear diameter at end-systole. Left ventricular end-diastolic diameter was measured from M-mode and 2-dimensional images obtained from parasternal long-axis views. The ratio of the E peak velocity to the average e′ peak velocity, using tissue Doppler imaging, was calculated at the septal side of the mitral annulus. Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment. Sites where a left ventricular intracavitary obstruction existed were localized by color Doppler echocardiography and pulsed-wave Doppler echocardiography. The definition of a left ventricular outflow tract obstruction (OTO) was indicated in previous studies.[1,2,4]

Study End Points

The study end point was HCM-related death defined by the following 3 types of cardiac events: (1) a combined end point of sudden death (unexpected death occurring in the absence of symptoms or within 1 hour of the onset of symptoms in patients with a relatively stable or uneventful course), successful resuscitation after a cardiac arrest (ventricular fibrillation or ventricular tachycardia with a pulseless collapse), or appropriate ICD shocks; (2) heart failure–related death in the context of progressive cardiac decompensation within 1 year before death, particularly if complicated by pulmonary edema or evolution to an end-stage phase, and advanced refractory heart failure in patients who received heart transplants that were considered equivalent to HCM-

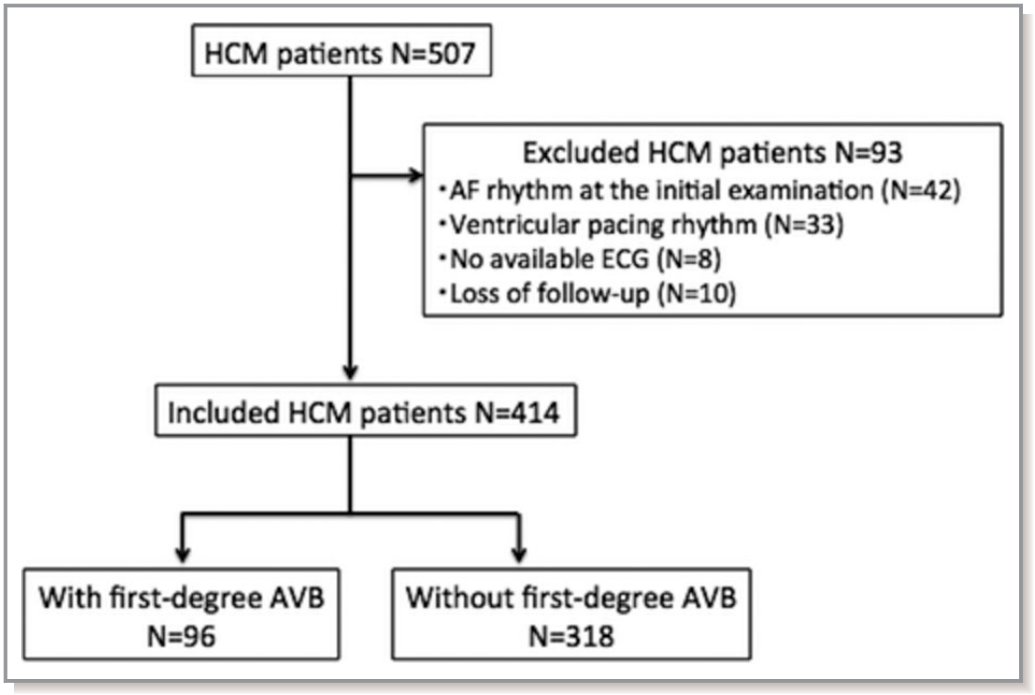

Figure 1. Flow chart of the enrolled HCM patients. AF indicates atrial fibrillation; AVB, atrioventricular block; HCM, hypertrophic cardiomyopathy.

related heart failure deaths in this analysis; and (3) stroke-related death, which occurred in patients who died as a result of an ischemic stroke.[3,4,6] These events were identified and classified at time of occurrence by experienced cardiologists and electrophysiologists and subsequently ascertained by the study investigators by reviewing the medical records.

Statistical Analysis

We retrospectively analyzed the clinical characteristics, P-R interval at the time of the initial evaluation, and outcomes during the follow-up. The results are presented as the mean±SD, median (interquartile range), or frequency (percentage). Student *t* tests were used to compare normally distributed continuous variables, and Mann–Whitney U tests were used to analyze skewed continuous or ordinal variables between groups. Nominal variables were compared using χ^2 tests or Fisher's exact tests (when an expected value was <5). Event-free curves were estimated using the Kaplan–Meier method, and differences between curves were assessed by log-rank tests. Uni- and multivariate Cox proportional hazards models were applied to evaluate the association of first-degree AVB to HCM-related death and the combined end point of sudden death or potentially lethal arrhythmic events. Variables with a *P* value of <0.05 for the univariate associations were entered into a step-wise multivariate Cox proportional hazards model to identify any independent predictors. For including all potential confounders in 1 multivariable model despite the small number of end points, we calculated the risk score for sudden cardiac death in the 2014 European Society of Cardiology guidelines[2] and used it as a single variable (combined 7 variables such as age at the time of the initial evaluation, a family history of sudden death, maximum left ventricular wall thickness, nonsustained ventricular tachycardia, unexplained syncope, OTO, and LAD into a single variable). Furthermore, in order to investigate the influence of potential causes of P-R prolongation, we used another multivariable model adjusted for an increased vagal tone, intraventricular conduction disorder, and presence of antiarrhythmic medications (ie, resting heart rate, QRS duration, and medication use such as β-blockers, calcium-channel antagonists, and amiodarone).[7,9] All tests were 2-sided, and statistical significance was set at a value of $P<0.05$. All statistical analyses were performed using SPSS software (version 23.0; SPSS, Inc, Chicago, IL).

Results

Distribution of the P-R Interval

The median (interquartile range) P-R interval among a total of 414 HCM patients was 172 (154–196) ms. Over a median follow-up period of 8.8 (4.9–12.9) years, 56 patients (13.5%) experienced HCM-related deaths. Among those, 47 patients (11.4%) had the combined end point of sudden death or potentially lethal arrhythmic events, including 17 patients (4.1%) with sudden death, 10 (2.4%) with successfully

resuscitated cardiac arrest (6 with documented ventricular fibrillation and 4 with documented ventricular tachycardia with a pulseless collapse), and 20 (4.8%) with appropriate ICD shocks. Among the remaining 9 patients, 6 (1.4%) experienced heart failure–related death, including 2 (0.5%) with heart transplantations, and 3 (0.7%) who experienced a stroke-related death. Median time from initial evaluation to HCM-related death was 5.9 (2.5–10.5) years.

Box and whisker plots of the P-R interval in patients without HCM-related deaths, with HCM-related deaths, and with the combined end point of sudden death or potentially lethal arrhythmic events are shown in Figure 2. Mean P-R interval in those with HCM-related death (190.4±42.5 ms) and the combined end points of sudden death or potentially lethal arrhythmic events (192.4±43.6 ms) were significantly longer than in those without HCM-related death (172.3±26.6 ms).

Baseline Characteristics According to Those With or Without First-Degree AVB

All patients were divided into 2 groups according to presence of first-degree AVB at the time of the initial evaluation. There were a total of 96 patients (23.2%) with first-degree AVB and 318 (76.2%) without first-degree AVB (Figure 1). Baseline clinical characteristics of the 2 groups are summarized in Table 1. Patients with first-degree AVB had a higher prevalence of OTO and a history of paroxysmal AF, larger LAD, and longer QRS duration than those without first-degree AVB. However, baseline New York Heart Association functional class, calculated HCM risk score for SCD,[2] medication use, and median follow-up period did not differ between the 2 groups.

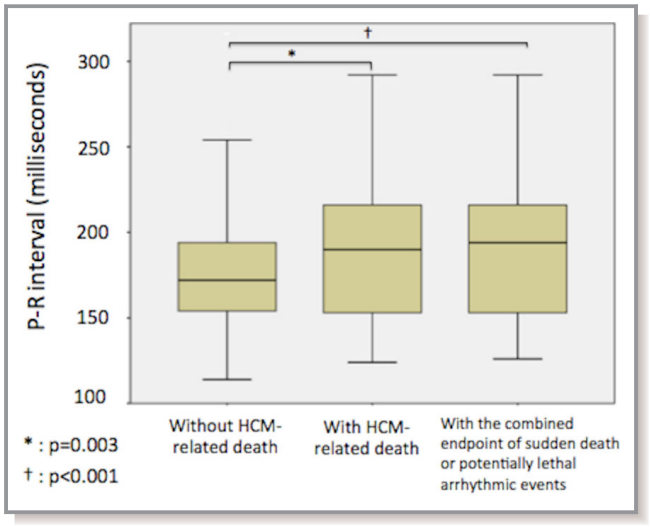

Figure 2. Box and whisker plots of the P-R intervals in HCM patients without any events, with HCM-related death, or with the combined end point of sudden death or potentially lethal arrhythmic events. The line across each box represents the mean P-R interval; the box represents the SD; and the I bars represent the 95% CIs. HCM indicates hypertrophic cardiomyopathy.

Clinical Outcomes According to Presence of First-Degree AVB

During the follow-up periods, 16 of the 96 patients with first-degree AVB (16.6%) and 19 of the 318 patients without first-degree AVB (6.0%) experienced new-onset AF (P=0.002; Figure 3A). Among patients with episodes of AF, catheter ablation was performed in 9 of the 96 patients with first-degree AVB (9.4%) and 21 of the 318 patients without first-degree AVB (6.6%; P=0.359). Episodes of unplanned hospitalizations attributed to progressive heart failure with an increase to a New York Heart Association 3 or 4 functional class occurred in 22 of the 96 patients with first-degree AVB (22.9%) and 28 of the 318 patients without first-degree AVB (8.8%; P=0.0002; Figure 3B). Episodes of nonfatal thromboembolic strokes occurred in 5 of the 96 patients with first-degree AVB (5.2%) and 13 of the 318 patients without first-degree AVB (4.1%), respectively (P=0.637; Figure 3C).

During the follow-up periods, 24 of the 96 patients with first-degree AVB (25.0%) experienced HCM-related deaths. Among those, 21 patients (21.9%) had the combined end point of sudden death or potentially lethal arrhythmic events, including 8 patients (8.3%) who experienced sudden death, 3 (3.1%) resuscitated after a cardiac arrest (1 with documented ventricular tachycardia with a pulseless collapse and 2 with documented ventricular fibrillation), and 10 (10.4%) with appropriate ICD shocks. Three patients (3.1%) had heart failure–related deaths, including 2 (2.1%) with heart transplantations. No stroke-related deaths were observed in this group. On the contrary, 32 of the 318 patients without first-degree AVB (10.1%) experienced an HCM-related death. Among those, 26 patients (8.2%) had the combined end point of sudden death or potentially lethal arrhythmic events, including 9 patients (2.8%) with sudden death, 7 (2.2%) resuscitated after a cardiac arrest (3 with documented ventricular tachycardia with a pulseless collapse and 4 with documented ventricular fibrillation), and 10 (3.1%) with appropriate ICD shocks. There were 3 patients (0.9%) who experienced heart failure–related deaths and 3 (0.9%) who experienced stroke-related deaths. Median time from initial evaluation to HCM-related death was 4.8 (2.2–10.4) years in those with first-degree AVB, whereas it was 8.0 (3.2–10.6) years in those without first-degree AVB. ICDs were finally implanted in 26 of the 96 patients with first-degree AVB (27.1%), including 23 for primary prevention and 3 for secondary prevention and 56 of the 318 patients without first-degree AVB (17.6%), including 50 for primary prevention and 6 for secondary prevention (P=0.041).

Table 1. Baseline Characteristics of HCM Patients With and Without First-Degree AVB

	Patients With First-Degree AVB (N=96)	Patients Without First-Degree AVB (N=318)	*P* Value
Age at the time of the initial evaluation, y	51.2±16.9	50.7±16.1	0.78
Male sex (%)	67 (69.8)	200 (62.9)	0.39
Outflow tract obstruction (%)	31 (32.3)	65 (20.4)	0.02
Hypertension (%)	41 (42.7)	127 (39.9)	0.63
Diabetes mellitus (%)	19 (19.8)	47 (14.8)	0.24
Ischemic heart disease (%)	7 (7.3)	20 (6.3)	0.73
History of paroxysmal atrial fibrillation (%)	21 (21.9)	41 (12.9)	0.03
Family history of sudden cardiac death (%)	12 (12.5)	44 (13.8)	0.74
Nonsustained ventricular tachycardia (%)	36 (37.5)	97 (30.5)	0.20
Unexplained syncope (%)	15 (15.6)	52 (16.4)	0.87
New York Heart Association functional class			0.70
I (%)	47 (49.0)	171 (53.8)	
II (%)	45 (46.9)	134 (42.1)	
III (%)	4 (4.2)	13 (4.1)	
Maximum left ventricular wall thickness, mm	18.7±4.7	19.5±5.2	0.18
Left ventricular end-diastolic dimension, mm	46.7±7.5	45.9±7.0	0.32
Left ventricular ejection fraction, %	53.4±11.0	55.1±9.8	0.25
Left atrial dimension, mm	40.8±9.2	38.0±7.5	0.009
E/e' at the septal mitral annulus	15.8±6.9	15.4±7.5	0.68
Calculated HCM risk/SCD at 5 y*			0.30
Low risk <4% (%)	66 (68.8)	242 (76.1)	
Moderate risk 4 to <6% (%)	14 (14.6)	40 (12.6)	
High risk ≧6% (%)	16 (16.7)	36 (11.3)	
Risk score (%)	2.5 (1.5–4.8)	2.3 (1.5–3.9)	0.42
Resting heart rate, /min	65.3±10.6	67.7±11.1	0.06
PR interval, ms	231.2±33.2	163.7±19.2	<0.001
QRS duration, ms	112.3±20.3	102.6±18.6	<0.001
Complete left bundle branch block (%)	3 (3.1)	5 (1.6)	0.33
Complete right bundle branch block (%)	9 (9.4)	25 (7.9)	0.64
SV1, mm	15.3±10.5	15.8±9.1	0.66
QRS axis, degrees	28.0±56.2	36.4±46.5	0.18
Treatment			
β-blockers (%)	71 (74.0)	215 (67.6)	0.24
Calcium-channel antagonist (%)	16 (16.7)	45 (14.2)	0.54
Amiodarone (%)	14 (14.6)	32 (10.1)	0.22
Septal reduction therapy (%)	8 (8.3)	20 (6.3)	0.49
Follow-up duration, y	8.3 (4.0–13.2)	8.9 (5.2–12.8)	0.43

All data are expressed as the mean±SD, n (%), or median (interquartile range). AVB indicates atrioventricular block; E, early transmitral filling velocity; e', early diastolic mitral annular velocity; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.
*2014 European Society of Cardiology guideline recommendation on an implantable cardioverter defibrillator implantation.

In the univariate analysis using the Kaplan–Meier method, patients with first-degree AVB had a significantly greater likelihood of an HCM-related death than those without first-degree AVB (log-rank, *P*=0.0003; Figure 4A). Probability of the combined end point of sudden death or potentially lethal arrhythmic events among patients with first-degree AVB was also significantly higher than that among those without first-degree AVB (log-rank, *P*=0.0003; Figure 4B). In a multivariable analysis that included the potential clinical predictors of life-threatening cardiac events, first-degree AVB was found to be

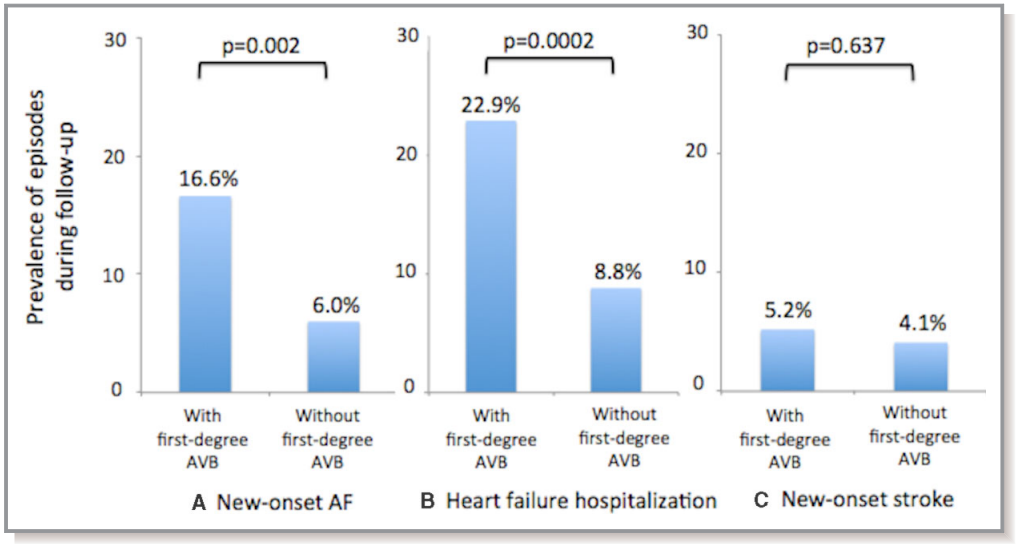

Figure 3. Prevalence of events that occurred during the follow-up period according to HCM patients with and without first-degree AVB. (**A**) New-onset AF, (**B**) unplanned hospitalizations attributed to progressive heart failure, and (**C**) new-onset nonfatal strokes. AF indicates atrial fibrillation; AVB, atrioventricular block; HCM, hypertrophic cardiomyopathy.

an independent correlate of either an HCM-related death (adjusted hazard ratio, 2.41; 95% CI, 1.27–4.58; *P*=0.007) or the combined end point of sudden death or potentially lethal arrhythmic events (adjusted hazard ratio, 2.60; 95% CI, 1.28–5.27; *P*=0.008; Table 2). Furthermore, even after an adjustment for the potential causes of P-R prolongation, first-degree AVB remained associated with an HCM-related death (adjusted hazard ratio, 2.32; 95% CI, 1.35–4.00; *P*=0.002) and a

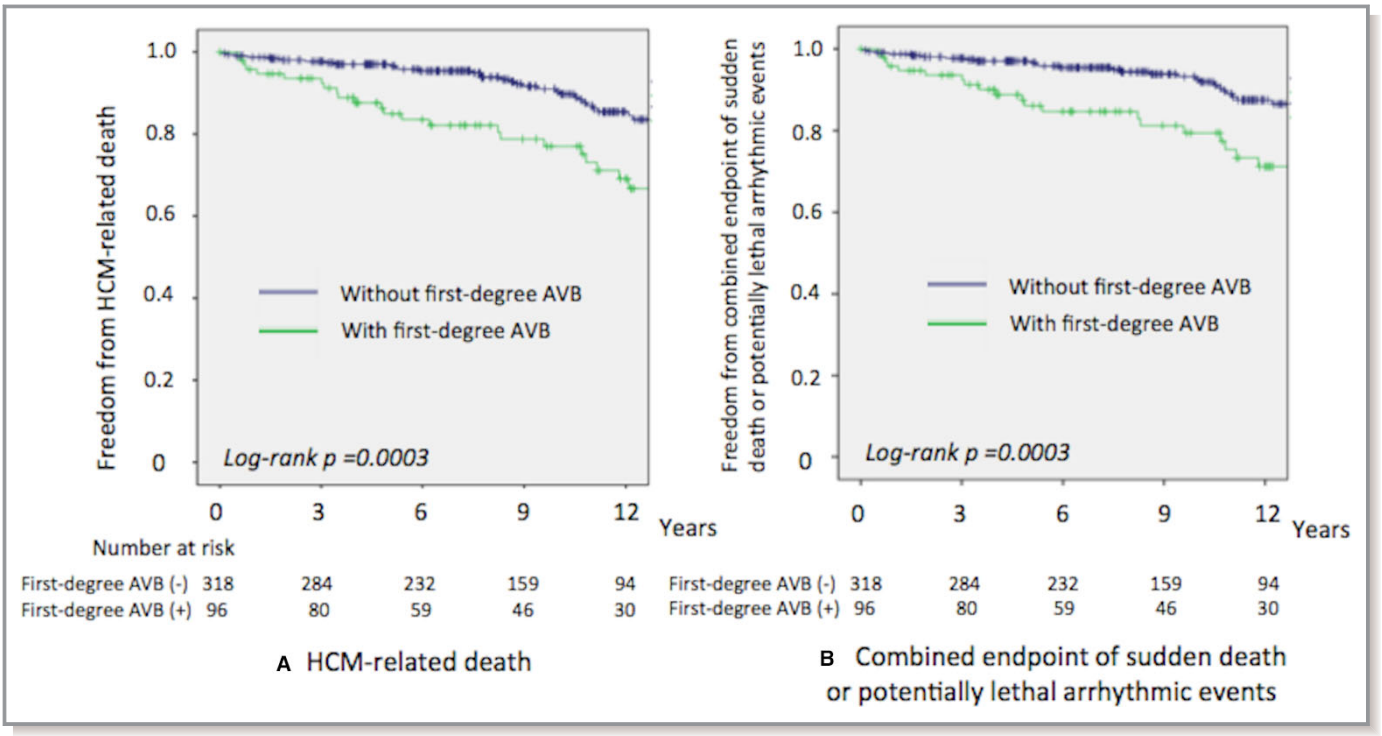

Figure 4. Kaplan–Meier estimates of the proportions of patients with HCM-related deaths in 96 patients with first-degree AVB and 318 patients without first-degree AVB. Cumulative probability of (**A**) HCM-related deaths and (**B**) the combined end point of sudden death or potentially lethal arrhythmic events in patients with and without first-degree AVB. AVB indicates atrioventricular block; HCM, hypertrophic cardiomyopathy.

Table 2. Adjusted HRs for HCM-Related Death and the Combined End Point of Sudden Death or Potentially Lethal Arrhythmic Events Associated With First-Degree AVB

	HCM-Related Death				The Combined End Point of Sudden Death or Potentially Lethal Arrhythmic Events			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Male sex	0.59 (0.35–1.00)	0.050	0.70 (0.35–1.38)	0.300	0.72 (0.41–1.28)	0.263		
Risk score for SCD at 5 y	1.09 (1.05–1.13)	<0.001	1.06 (1.00–1.11)	0.034	1.10 (1.06–1.14)	<0.001	1.07 (1.01–1.13)	0.013
History of paroxysmal AF	1.46 (0.75–2.82)	0.262			1.41 (0.68–2.93)	0.350		
Left ventricular ejection fraction	0.93 (0.91–0.96)	<0.001	0.95 (0.92–0.98)	0.002	0.94 (0.91–0.97)	<0.001	0.96 (0.93–1.00)	0.034
Septal E/e' ratio	1.05 (1.02–1.08)	0.001	1.03 (0.99–1.06)	0.150	1.05 (1.02–1.09)	0.001	1.03 (0.99–1.07)	0.104
NYHA functional class	1.66 (1.06–2.61)	0.028	0.87 (0.48–1.57)	0.642	1.73 (1.06–2.82)	0.029	1.05 (0.56–1.97)	0.874
QRS duration	1.01 (1.00–1.02)	0.066			1.01 (1.00–1.02)	0.024	1.00 (0.98–1.01)	0.708
First-degree AVB	2.56 (1.51–4.36)	<0.001	2.41 (1.27–4.58)	0.007	2.76 (1.55–4.91)	0.001	2.60 (1.28–5.27)	0.008

AF indicates atrial fibrillation; AVB, atrioventricular block; E, early transmitral filling velocity; e', early diastolic mitral annular velocity; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; NYHA, New York Heart Association; SCD, sudden cardiac death.

combined end point of sudden death or potentially lethal arrhythmic events (adjusted hazard ratio, 2.51; 95% CI, 1.39–4.53; *P*=0.002).

Established risk factors for sudden cardiac death[1] of the study patients with HCM with and without a combined end point of sudden death or potentially lethal arrhythmic events are listed in Table 3. Although 17 of 47 patients (36.2%) with the end point had no established risk factors for sudden death, 12 of those 17 patients had first-degree AVB and only 5 (10.6%) were missed by the combination of established risk factors and presence of first-degree AVB. By adding the presence of first-degree AVB to the established risk factors, the accuracy of the risk stratification from the combined end point of sudden death or potentially lethal arrhythmic events improved from 36.2% to 10.6% (difference in the risk stratification accuracy of 25.6%; *P*=0.004).

Impact of First-Degree AVB on HCM-Related Death Among Those With and Without an OTO Phenotype

We also analyzed the probability of HCM-related death according to the presence of first-degree AVB among those with and without an OTO, respectively. There were a total of 96 patients with an OTO phenotype (23.2%) and 318 without an OTO phenotype (76.8%). Among those with an OTO

Table 3. Established Risk Factors for Sudden Death in the Study Patients With HCM With and Without the Combined End Point of Sudden Death or Potentially Lethal Arrhythmic Events

	With the End Point (N=47)	Without the End Point (N=367)	*P* Value
Left ventricular wall thickness≧30 mm	5 (10.6)	18 (4.9)	0.106
Family history of sudden cardiac death	13 (27.7)	43 (11.7)	0.003
Unexplained syncope	13 (27.7)	54 (14.7)	0.023
Nonsustained ventricular tachycardia	21 (44.7)	112 (30.5)	0.050
No. of established risk factors			<0.001
0	17 (36.2)	190 (51.8)	
1	13 (27.7)	133 (36.2)	
2	12 (25.5)	38 (10.4)	
3	5 (10.6)	6 (1.6)	
First-degree AVB	21 (44.7)	75 (20.4)	<0.001
First-degree AVB without an established risk factor	12 (25.5)	37 (10.1)	0.002

All data are expressed as the n (%). AVB indicates atrioventricular block; HCM, hypertrophic cardiomyopathy.

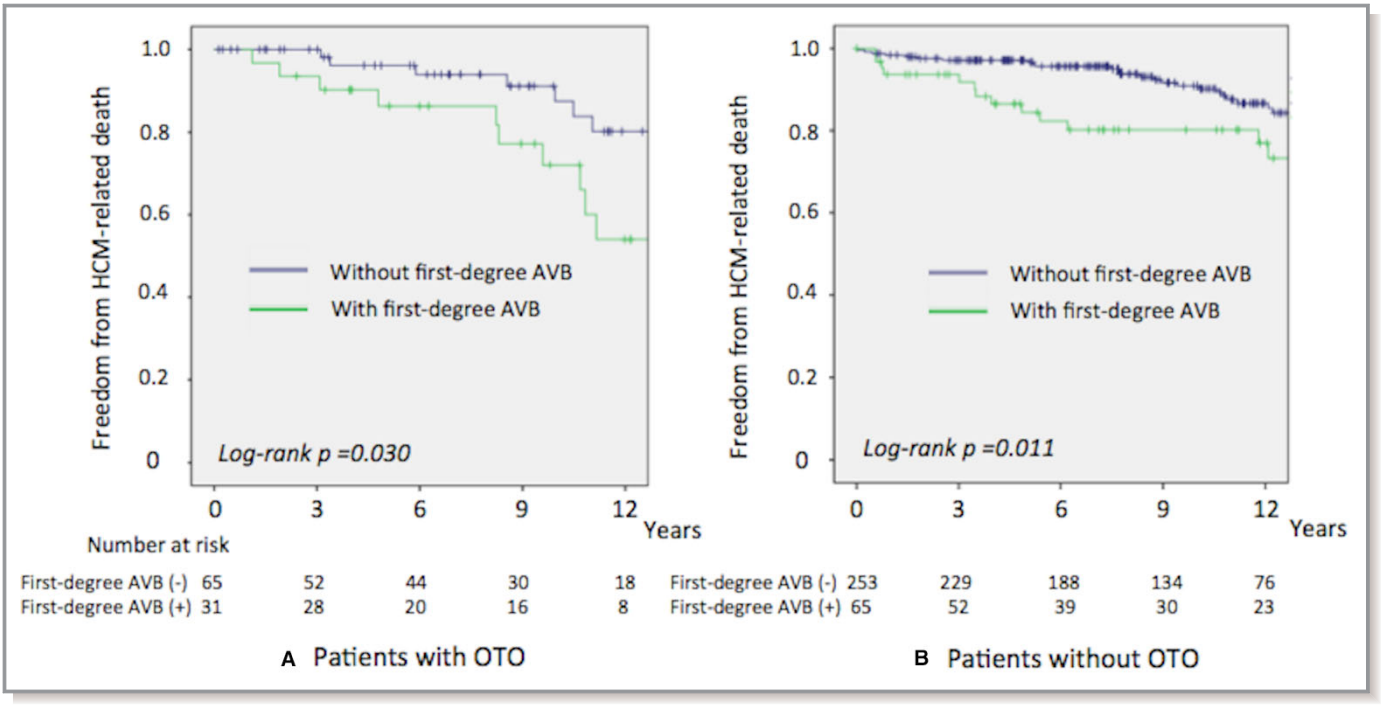

Figure 5. Kaplan–Meier estimates of the proportions of patients with HCM-related deaths with or without first-degree AVB according to presence of an OTO. Cumulative probability of an HCM-related death among (**A**) those with an OTO and (**B**) those without an OTO in patients with and without first-degree AVB. AVB indicates atrioventricular block; HCM, hypertrophic cardiomyopathy; OTO, outflow tract obstruction.

phenotype, patients with first-degree AVB had a significantly greater likelihood of an HCM-related death than the patients without first-degree AVB (log-rank, *P*=0.030; Figure 5A). Furthermore, among those without an OTO phenotype, patients with first-degree AVB also had a significantly greater likelihood of an HCM-related death than those without first-degree AVB (log-rank, *P*=0.011; Figure 5B).

Discussion

First-degree AVB is frequently encountered in clinical practice. According to a recent systematic review, prevalence of first-degree AVB ranges from 2% to 14% and mean prevalence is 7% in the total population.[10] When focusing on patients with organic heart disease, first-degree AVB becomes more prevalent, such as 10% in patients with stable coronary artery disease,[12] 23% in patients with persistent AF,[13] and 24% in patients with arrhythmogenic right ventricular cardiomyopathy.[14] Furthermore, a recent systematic review showed that among a total of 21 710 patients who were implanted with a cardiac resynchronization therapy device, 20% of patients contracted first-degree AVB.[15] This high prevalence may be linked to their myocardial conduction system fibrosis and conduction abnormalities or the necessity for medication use that involves a conduction delay in the atrioventricular nodes. In our HCM cohort, first-degree AVB was also found in 23%, which seemed to be similar to that in those with other organic heart diseases. Furthermore, the median P-R interval among a total of 414 patients in our study was 172 (154–196) ms. According to the previous studies in HCM patients, the median P-R interval was within a range of 171 to 182 ms, suggesting that our results were consistent with those results.[18–21]

Maron et al previously reported that the annual event rate of HCM-related deaths in a large cohort of 744 patients with HCM was 1.40%.[3] The latest study indicated that annual HCM-related morality rate improved to 0.53%, and 0.79% of events in patients could be treated as potentially lethal events such as appropriate ICD interventions, heart transplantations, and resuscitated out-of-hospital cardiac arrests.[6] In the present study, incidence of HCM-related deaths was 1.57% per year, but it included 0.90% of aborted events, which was the same as the potentially lethal events in the latest study. Therefore, the results of this study may have consistency and generalizability, providing additional epidemiological information on first-degree AVB and the HCM-related death rate in a relatively large longitudinal cohort of patients with HCM.

Several studies have reported ECG-derived risk factors for sudden cardiac death in the HCM population.[18,21–23] However, to the best of our knowledge, there has not been any study reporting the impact of first-degree AVB on the worse prognosis. Patel et al and Haghjoo et al both reported that first-degree AVB was not associated with risk of SCD in patients with HCM.[21,22] Though the discrepancy between their studies and our study remains unclear, it may be caused

by the differences in their follow-up periods. The mean follow-up period in the report of Patel et al was 2.5 years and in the report of Haghjoo et al was 4.2 years. In contrast, the mean follow-up period in our study was 8.8 years, and the median time from initial evaluation to HCM-related death was 5.9 years.

The mechanism that underlies the association between first-degree AVB and adverse cardiovascular outcomes and mortality is unclear. However, there are some possible explanations for the association between presence of first-degree AVB and HCM-related death in patients with HCM. In the present study, an enlarged LAD was much more frequently found in patients with first-degree AVB than in those without first-degree AVB. Several studies have reported that an increased left atrial (LA) size is considered a marker of HCM disease severity and an independent predictor of an SCD.[2,24–26] The latest European Society of Cardiology guidelines have included an enlarged LAD as a factor of the new risk prediction model for SCD.[2] The pathogenesis of LA enlargement in patients with HCM is likely multifactorial. Diastolic dysfunction, left ventricular intracavitary obstructions, mitral regurgitation, elevated left ventricular filling pressures, and episodes of AF lead to LA remodeling and dilation. Previous studies reported that a P-R prolongation has negative hemodynamic effects, such as a shortening of blood filling time and diastolic mitral valve regurgitation.[27–31] In a subset of patients, onset of atrial depolarization occurs just after the previous ventricular contraction, leading to shortening of blood filling time to the ventricle.[27,28] This could adversely affect both left ventricle and LA filling pressure, resulting in a further volume overload in the LA. Furthermore, in the setting of inappropriate atrioventricular coupling, a prolonged left ventricular filling period increases left ventricular pressure toward end-diastole. This causes a delayed and ineffective mitral valve closure and consequent diastolic mitral regurgitation, leading to a further volume overload in the LA.[29–31] In our study, new-onset AF and unplanned hospitalizations attributed to progressive heart failure in those with first-degree AVB occurred >2-fold as frequently as in those without first-degree AVB during the follow-up period. The increasing pressure and volume overload attributed to the P-R prolongation might lead to the likely formation of an advanced atrial arrhythmogenesis and clinical exacerbation of heart failure.

On the contrary, first-degree AVB may be a manifestation of an advanced remodeling in the HCM heart. Ausma et al previously reported that a prolonged conduction time reflects a comprehensive estimation of both advanced structural and electrical remodeling.[32] The P-R interval is determined by conduction time from the sinus node to the ventricles and thus integrates information about a number of sites in the conduction system of the heart.[7–9] Therefore, first-degree AVB reflects not only a conduction delay in the atrioventricular node, but also the conduction abnormalities involving any part of the conduction system.[7–9] In patients with HCM, an enlarged atrial dimension is a major factor of structural remodeling that may lead to a P-R prolongation. Recently, Schumacher et al reported that a P-R prolongation might be associated with extent of atrial fibrosis.[13] Furthermore, Oloriz et al reported that in patients with nonischemic cardiomyopathy, a P-R prolongation might be correlated with myocardial fibrosis observed in the ventricular septum.[33] All these reports suggested that first-degree AVB might be a manifestation of advanced electrical remodeling involving either the atrium or ventricle, and these electrical abnormalities might increase vulnerability to arrhythmia and lead to a worse prognosis in patients with HCM. However, in the present study, there was no significant difference between patients with and without first-degree AVB regarding the septal ratio of the E peak velocity to the average e′ peak velocity, which might be a potential surrogate of diastolic function. Further studies are needed to investigate the association between severity of ventricular fibrosis and consequent first-degree AVB.

Evaluating the P-R interval has advantages in that it can be measured easily and quickly in all clinical situations with a low cost and high reproducibility. Therefore, it may be useful for the generalists to judge the need for referrals to tertiary centers for HCM. In addition, new emerging first-degree AVB may be used as a sign in need of an evaluation whether patients have silent disease progression. Furthermore, in cases with an equivocal indication for ICD therapy, first-degree AVB may be a potentially useful marker for optimizing their decisions.

Limitations

First, the present study was based on the retrospective enrollment of individual patients with HCM, which is an unavoidable limitation shared by virtually all large-scale clinical studies on HCM. This study was evaluated in a single tertiary referral center in Japan and was therefore subject to selection bias by including a highly selected population of patients with HCM. Therefore, our results may not have determined definitely that first-degree AVB is a better sudden-death risk-stratification marker than the conventional risk markers. Second, despite adjustments by multivariable analyses, we cannot completely exclude the possibility of residual confounding factors of the association between first-degree AVB and adverse cardiovascular outcomes by unmeasured variables. The number of patients who reached the combined end point was low at 56 cases, which may make our multivariable analysis less statistically robust. Furthermore, the number of each patient with an end point of HCM-related

death, especially for heart failure–related deaths and stroke-related deaths, was not adequate to evaluate the association between first-degree AVB and adverse cardiovascular outcomes separately. Therefore, further population-based, multicenter, and multinational studies are required to confirm and extend our findings. Third, we did not measure myocardial fibrosis by contrast-enhanced cardiovascular magnetic resonance imaging at the time of the initial evaluation in all study patients with HCM. In addition, we did not perform invasive electrophysiological studies to determine the relative contribution of each component of the P-R interval. Finally, P-R intervals were measured at only 1 time point, but were not measured during the follow-up. Therefore, the prognostic effect of serial P-R interval measurements in patients with HCM is unclear.

Conclusions

In this cohort of patients with HCM, first-degree AVB may be associated with an increased risk of HCM-related death, including the combined end point of sudden death or potentially lethal arrhythmic events. This simple and practical marker may be useful to stratify risk of life-threatening events and make better management decision in patients with HCM. However, because of the retrospective, single-center study design with the small number of end points, our results must be considered quite preliminary. Furthermore, prospective, multicenter, larger-scale studies are needed to confirm and extend the current findings on the relationship between first-degree AVB and life-threatening cardiac events in patients with HCM.

Acknowledgments

We thank Mr John Martin for his linguistic assistance in the preparation of the manuscript.

Disclosures

None.

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