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Future bradyarrhythmia in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: A few studies to evaluate an incidence of bradyarrhythmia in patients with hypertrophic cardiomyopathy (HCM) have been reported.
Methods: We enrolled 161 patients with HCM to evaluate their bradyarrhythmia risk, especially the risk of patients who were at risk for sudden cardiac death (SCD) and eligible for implantation of an implantable cardiac defibrillator (ICD). We defined symptomatic bradyarrhythmia requiring a pacing therapy as a bradyarrhythmia event and collected the data on an occurrence of the event after the time of diagnosis of HCM. The incidence of bradyarrhythmia events was compared between patients with ICD indications (ICD-candidate group) and those without (non-ICD-candidate group). Furthermore, we investigated the associated factors with bradyarrhythmia events using a Cox proportional-hazards model.
Results: During 5.5 ± 4.4 years follow-up, bradyarrhythmia events occurred in 8% (13 patients) of whole patients, and in 15% of the ICD-candidate group (n = 74). In contrast, only 2 events (2%) occurred in the non-ICD-candidate group. The incidence of bradyarrhythmia in the ICD-candidate group was significantly higher than that in the non-ICD-candidate group (log-rank p = 0.015). In the ICD-candidate group, a Cox proportional-hazards model demonstrated that lower heart rate at the time of diagnosis (HR: 1.072, 95% CI: 1.012 to 1.135, p = 0.018), and an eligibility of ICD implantation for secondary prevention of SCD (HR: 9.092, 95%CI: 2.644 to 31.258, p < 0.001) were significantly associated with future bradyarrhythmia.
Conclusions: HCM patients with eligibility for ICD implantation, especially for secondary prevention of SCD, more frequently suffered from bradyarrhythmia events.

1. Introduction

Sudden cardiac death (SCD) derived from fatal ventricular tachyarrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF) is a major concern for patients with hypertrophic cardiomyopathy (HCM) [1]. Implantation of an implantable cardioverter-defibrillator (ICD) is strongly recommended to prevent SCD for these patients [2,3]. Recently, a subcutaneous ICD (S-ICD) has become available to prevent SCD for these patients and the number of implantation of S-ICD is increasing because its efficacy and safety are comparable to conventional transvenous ICD (TV-ICD) for patients with a risk of SCD [4–6]. The prevention of an endovascular infection related to implanted ICD is known as a particularly notable benefit of S-ICD implantation and S-ICD is preferred despite its incapability of pacing therapy [7–9].

There were only few reports about a symptomatic bradyarrhythmia due to sick sinus syndrome (SSS) or atrioventricular block (AVB) in patients with HCM [10], and the estimation of bradyarrhythmia risk in patients with HCM has not been elucidated well. Therefore, we conducted this study to investigate the incidence of bradyarrhythmia complications in patients diagnosed as HCM, especially in HCM patients who need an implanted ICD device to prevent fatal ventricular tachyarrhythmias.

2. Methods

Consecutive 161 adult patients (≥20 years) who were diagnosed as idiopathic HCM in our institution between January 2002 and June 2018 were retrospectively included in this study. The diagnosis of HCM was based on the criteria given in the guidelines [11] as follows: the presence of left ventricular (LV) wall thickness ≥ 15 mm, or ≥ 13 mm with a family history of HCM, and the absence of cardiac hypertrophy due to infiltrative cardiomyopathy. When the diagnosis required a histological evaluation to differentiate infiltrative cardiomyopathy as well as

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hypertensive heart disease from HCM, we used endomyocardial biopsy for the diagnosis. Patients with asymmetric LV hypertrophy confined predominantly the LV apex (apical subtype), which showed LV wall thickness ≥ 15 mm and maximal apical wall thickness >1.5 times of the posterior wall thickness, were also included in study patients [12,13]. Assessments of LV wall morphology and LV wall thickness, as well as measurements of LV ejection fraction (LVEF), were performed with echocardiography or cardiac magnetic resonance imaging. The patients with end-stage HCM, showing severely-reduced exercise tolerance due to heart failure symptoms (NYHA functional class IV), were excluded.

We collected data on demographics, laboratory values including brain natriuretic peptide (BNP) levels, medication, echocardiographic findings, and 12-lead electrocardiogram findings from the medical records of study patients. We also assessed the value of an individualized SCD risk prediction index (HCM Risk-SCD) of each study patient advocated by O'Mahony et al. [14]; it was calculated using the following parameters: maximal LV wall thickness, left atrial diameter, maximal LV outflow tract gradient, family history of SCD, history of NSVT, the experience of syncope, age at acquisition of ICD indications. The values of HCM Risk-SCD of the ICD-candidate group were assessed at the time when study patients were considered as candidates for implantation of ICD and those of the non-ICD-candidate group were done at the time of enrollment of this study. Additionally, we collected data about symptomatic bradyarrhythmia requiring pacemaker implantation due to SSS, AVB, or atrial fibrillation (AF) with a slow ventricular response (AF bradycardia) defined as an adverse bradyarrhythmia event of this study. The follow-up period was defined as the time from the date of HCM diagnosis to the occurrence of a bradyarrhythmia event or the last censoring when patients survived without bradyarrhythmia events. When the patients had already received pacemaker implantation until enrollment, we excluded them from the prognosis analysis. If the patients had received an ICD implantation to prevent SCD except for pacing therapy until the time of enrollment, symptomatic bradyarrhythmia requiring pacing therapy by implanted ICD device was defined as a bradyarrhythmia event for them. When a pacing therapy by the ICD device with predetermined lowest pacing rate was documented in the patients, their attending physicians determined the need for a pacing therapy by the ICD based on the requirement of more than 40 beat per minute pacing during their waking hours, which was equivalent to having symptoms. And then, if necessary, the physicians confirmed the development of symptoms derived from the bradyarrhythmia by a temporary halt of the pacing therapy of ICD. Furthermore, when the patients died for whatever reasons except for a severe bradyarrhythmia event during the follow-up period, they were considered censored cases in the prognosis analysis of this study.

We investigated the incidence of a bradyarrhythmia event in whole study patients. It was compared between the patients who were eligible for ICD implantation for the prevention of SCD (ICD-candidate group) and the patients who were at lower risk for SCD not to need ICD implantation (non-ICD-candidate group). The ICD indication was recommended by the Japanese Circulation Society based on the risk factors of SCD as follows: prior cardiac arrest, sustained VT (SVT) or VF, family history of SCD or aborted SCD, unexplained syncope, non-sustained VT (NSVT), maximal LV wall thickness ≥30 mm, or abnormal exercise blood pressure response. Regarding unexplained syncope, we evaluated the backgrounds of that using electrophysiological study and cardiac catheterization for measurement of intracardiac pressure. When the patients showed at least one risk factor despite no experience of cardiac arrest, SVT or VF, the guideline recommended for them to undertake an ICD implantation for primary prevention [15].

Besides, to search the associated factors with a bradyarrhythmia event in whole study patients as well as those of the ICD-candidate group, we evaluated the relative hazard of clinical variables experiencing a bradyarrhythmia event using a univariate Cox proportional-hazards model. For the analysis of bradyarrhythmia events in the ICD-candidate group, the follow-up period started at the time when the patients first became recognized their eligibilities for an ICD implantation under the guideline recommendation [15].

2.1. Statistical analysis

Patient characteristics are presented as means ± standard deviations for continuous variables and as proportions and percentages for categorical variables. We compared continuous variables using Student's t-test or Mann-Whitney U tests as applicable after normality tests. Pearson's chi-square test was used to compare the categorical variables. The incidence rate of bradyarrhythmia events was calculated by the person-year method. When the incidences were compared between the ICD-candidate and non-ICD-candidate groups, event-free survival curves from bradyarrhythmia events were drawn using the Kaplan-Meier method, and a log-rank test was used. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

We performed all statistical analyses using the JMP software, version 12.0 (SAS Institute Inc., Cary, NC, USA). This study was conducted in full accordance with the Declaration of Helsinki, and it received approval from the institutional review boards and ethics committees of the Nagoya City University Graduate School of Medical Sciences.

3. Results

3.1. Patient characteristics

The baseline characteristics of whole patients are shown in the left side of Table 1. The mean age was 64.5 ± 14.9 years, and 66 patients (41%) were female. Among all, 42 patients (26%) had intraventricular obstruction: mid-ventricular obstruction in 9 and left ventricular outflow tract obstruction in 33. Fifty-nine patients (37%) showed apical hypertrophy. Mean LVEF was 70 ± 10%, and the median of BNP levels was 181 pg/ml (interquartile range: 84–493 pg/ml).

Fig. 1 demonstrated the eligibility decision for an ICD implantation to prevent SCD in this study. At the time of enrollment of this study, 44 patients had ICD indications based on prior SVT or VF (n = 5), family history of SCD, SVT, or VF (n = 14), unexplained syncope (n = 12), NSVT (n = 7), maximal LV wall thickness ≥ 30 mm (n = 2), and abnormal exercise blood pressure response (n = 4). Additionally, 30 patients became considered as new candidates eligible for an ICD implantation during a follow-up period based on the experience of SVT or VF (n = 8), unexplained syncope (n = 3), and NSVT (n = 19). Finally, the total number of patients who acquired ICD indications (the ICD-candidate group) reached 74 patients: 13 patients were candidate for secondary prevention and 61 patients were for primary prevention.

We compared clinical characteristics between the ICD-candidate and non-ICD-candidate groups at the time of enrollment. (the right side of Table 1) Compared to the non-ICD-candidate group, the ICD-candidate group showed a lower estimated glomerular filtration rate (eGFR) (63.8 ± 19.8 vs. 68.5 ± 25.2 ml/min/1.73 m^2, p = 0.049), higher BNP levels (log BNP: 5.46 ± 1.18 vs. 4.97 ± 1.16 pg/ml, p = 0.016), thicker LV posterior wall (13 ± 3 vs 12 ± 2 mm, p = 0.036), larger left atrial diameter (42 ± 8 vs. 38 ± 9 mm, p = 0.006), and more frequent occurrence

Table 1
Clinical characteristics of study patients at diagnosis.

	Whole (n = 161)	ICD-candidate (n = 74)	Non-ICD-candidate (n = 87)	p-value
Age, years	64.5 ± 14.9	63.8 ± 14.9	65.0 ± 15.0	0.598
Female	66 (41.0)	29 (39.2)	37 (42.5)	0.668
Hypertension	85 (52.8)	39 (52.7)	46 (52.9)	0.983
Diabetes mellitus	26 (16.1)	13 (17.6)	13 (14.9)	0.652
Atrial fibrillation	23 (14.3)	13 (17.6)	10 (11.5)	0.270
Hospitalization for HF	33 (20.5)	19 (25.7)	14 (16.1)	0.143
eGFR, ml/min/1.73 m^2	66.6 ± 23.2	63.8 ± 19.8	68.5 ± 25.2	0.049
BNP (median, [IQR]), pg/ml	181 [84, 493]	262 [111, 622]	155 [61, 344]	NA
Log BNP, pg/ml	5.23 ± 1.18	5.46 ± 1.18	4.97 ± 1.16	0.016
Echocardiographic findings				
LVEF, %	70 ± 10	70 ± 10	71 ± 9	0.319
IVST, mm	15 ± 5	16 ± 6	14 ± 4	0.059
LVPWT, mm	12 ± 3	13 ± 3	12 ± 2	0.036
Maximal LVWT, mm	19 ± 5	19 ± 5	18 ± 4	0.067
LAD, mm	40 ± 9	42 ± 8	38 ± 9	0.006
Obstruction				
Mid-ventricular	9 (5.6)	7 (9.5)	2 (2.3)	0.049
LVOT	33 (20.5)	11 (14.9)	22 (25.3)	0.103
Apical subtype	59 (36.6)	24 (32.4)	35 (40.2)	0.639
ECG findings				
Heart rate, bpm	69 ± 14	67 ± 15	71 ± 13	0.055
QRS duration, ms	103 ± 18	105 ± 18	101 ± 18	0.205
HCM Risk-SCD score	2.23 ± 1.03	2.83 ± 0.61	1.78 ± 0.46	<0.001
Medications				
At the time of diagnosis				
Amiodarone	3 (1.9)	3 (4.1)	0 (0)	0.095
Class I antiarrhythmic agents	19 (11.8)	6 (8.1)	13 (14.9)	0.224
Beta-blocker	47 (29.2)	28 (37.8)	19 (21.8)	0.036
ACEI/ARB	51 (31.7)	29 (39.2)	22 (25.3)	0.064
At the time of last censoring				
Amiodarone	20 (12.4)	18 (24.3)	2 (2.3)	<0.001
Class I antiarrhythmic agents	26 (16.1)	10 (13.5)	16 (18.4)	0.402
Beta-blocker	90 (55.9)	49 (66.2)	41 (47.1)	0.015
ACEI/ARB	76 (47.2)	39 (52.7)	37 (42.5)	0.198

Values are given as the *n* (%) or mean ± standard deviation.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; IVST, interventricular septal thickness; IQR, inter-quartile range; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVPWT, left ventricular posterior wall thickness; LVWT, left ventricular wall thickness; SCD, sudden cardiac death; NA, not applicable.

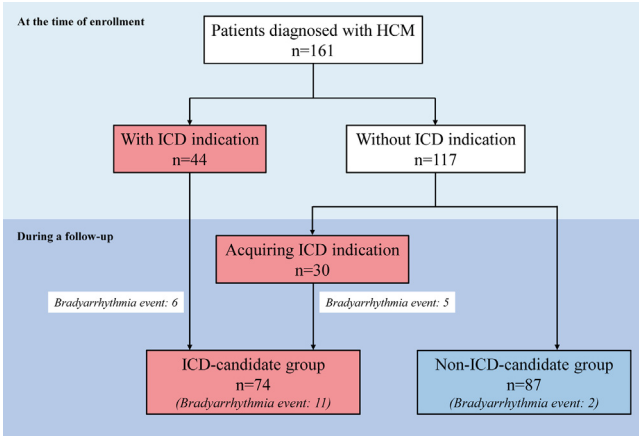

Fig. 1. Eligibility decision for ICD implantation to prevent SCD in HCM patients and the number of bradyarrhythmia events. At the enrollment of this study, 44 patients had implantable ICD indications. And, 30 patients became considered as new candidates eligible for ICD implantation during a follow-up period. These patients were included the ICD-candidate group. (painted box in red) On the other hand, the patients who had not acquired ICD indications during follow-up period were a total 87 patients and included in the non-ICD-candidate group. (painted box in blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of a mid-ventricular obstruction (9.5% vs. 2.3%, p = 0.049). Regarding the medication at the time of enrollment, a beta-blocker was more frequently prescribed in patients of the ICD-candidate group than those of the non-ICD-candidate group (37.8% vs. 21.8%, p = 0.036). Amiodarone usage was similar between the 2 groups. In contrast, regarding to the administration of these drugs at the time of last censoring, beta-blocker and amiodarone were more frequently prescribed in patients of the ICD-candidate group (Beta-blocker: 66.2% vs. 47.1%, p = 0.015; Amiodarone: 24.3% vs. 2.3%, p < 0.001, respectively). In the ECG findings such as heart rate and QRS duration, no significant difference between the 2 groups at the time of enrollment was found.

3.2. Incidence of bradyarrhythmia events

During 5.5 ± 4.4 years of follow-up, bradyarrhythmia events occurred in 13 patients (8%) of whole patients, and the incidence of the events was 1.55 per 100 person-years. No patient had received pacing therapy before his/her diagnosis of HCM. A total of 21 patients died due to any reasons except a serious bradyarrhythmia. No patient received a surgical myectomy or a percutaneous transluminal septal myocardial ablation for LV outflow tract obstruction, which had potential risk for iatrogenic bradyarrhythmia such as AVB during a follow-up period.

In the non-ICD-candidate group, only 2 (2%) bradyarrhythmia events occurred. In contrast, the ICD-candidate group showed 11

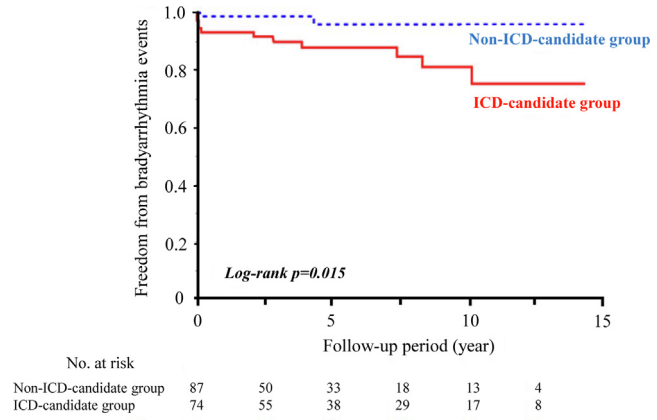

Fig. 2. Comparison of bradyarrhythmia event free survival between the ICD-candidate and non-ICD-candidate groups. Compared to the non-ICD-candidate group, the ICD-candidate group demonstrated significantly worse bradycardia event-free survival (log-rank test, $P = 0.015$).

events (15%) during a follow-up period. (Fig. 1) According to the comparison of a bradyarrhythmia event-free survival curves between the ICD-candidate and non-ICD-candidate groups, the ICD-candidate group demonstrated a significantly worse survival (log-rank test, $P = 0.015$) (Fig. 2) and a higher incidence of bradyarrhythmia events with 2.4 per 100 person-years (vs. 0.5 per 100 person-years in the non-ICD-candidate group).

3.3. Risk factors for bradyarrhythmia events in HCM

The relative hazards of clinical variables experiencing a bradyarrhythmia event were demonstrated by using a univariate Cox proportional hazards model in whole study patients and the ICD-candidate group in Table 2. In whole study patients, female sex had a hazard ratio (HR) 1.877 with 95% confidence interval (CI) 1.037 to 3.396 (p = 0.037), higher BNP levels had a HR 1.982 with 95% CI 1.156 to 3.401 (p = 0.013), and lower heart rate had a HR 1.071 with 95% CI 1.010 to 1.136 (p = 0.022), respectively. Additionally, an ICD indication (especially for secondary prevention) had a HR 5.387 with 95% CI 1.188 to 24.430 (p = 0.029) (secondary prevention: HR 12.890 with 95% CI 4.270 to 38.910, p < 0.001), respectively.

Focused on the ICD-indication group, we demonstrated that lower heart rate had a HR 1.072 with 95% CI 1.012 to 1.135 (p = 0.018), and an ICD indication for secondary prevention had a HR 9.092 with 95% CI 2.644 to 31.258 (p < 0.001), respectively.

3.4. Clinical features of patients with bradyarrhythmia events in the ICD-candidate group

The summary of the clinical course of 11 patients in the ICD-candidate group who experienced bradyarrhythmia events during a follow-up period was shown in Table 3. In summary, 3 featured properties of these patients came out. First, almost all patients (10/11) experienced bradyarrhythmia events due to SSS and one patient due to AF bradycardia. Second, more than half of the patients (7/11) experienced bradyarrhythmia events within only 1 year after becoming eligible for an ICD implantation. In contrast, the rest (4/11) had the events several years later. Third, among the 7 patients who experienced a rapid progression of bradyarrhythmia, one patient was required to change the ICD device from S-ICD to TV-ICD for needed pacing therapy, although she received implantation of S-ICD as an initial implanted device due to severe systemic atopic dermatitis.

4. Discussion

To the best of our knowledge, this study is the first investigation regarding details of bradyarrhythmia events requiring pacemaker implantation in patients with HCM. The main findings were as follows: 1) During 5.5 years follow-up, 8% of HCM patients experienced bradyarrhythmia events requiring pacing therapy; 2) The patients with eligibility for an ICD implantation were more frequently experienced a bradyarrhythmia event than those without; 3) Especially, lower heart rate at the time of diagnosis, and a prior SVT or VF were associated with a progression of bradyarrhythmia among patients with ICD indications; and 4) Symptomatic SSS was the primary cause of bradyarrhythmia events in patients with HCM and ICD indications.

HCM patients have various concomitant issues such as AF, congestive heart failure, and fatal ventricular tachyarrhythmias, then

Table 2
Contribution of clinical variables to bradyarrhythmia events in HCM.

	Whole		ICD-candidate group	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years		0.297		0.058
Female	1.877 (1.037–3.396)	0.037		0.067
Hypertension		0.576		0.495
Diabetes mellitus		0.293		0.299
Atrial fibrillation		0.468		0.344
Hospitalization of HF		0.157		0.980
eGFR, ml/min/1.73 m^2		0.121		0.161
Log BNP, pg/ml	1.982 (1.156–3.401)	0.013		0.142
LVEF, %		0.723		0.872
Maximal LVWT, mm		0.054		0.145
LAD, mm		0.700		0.903
Obstruction				
Mid-ventricular		0.771		0.965
LVOT		0.248		0.648
Apical subtype		0.137		0.358
Heart rate, bpm	1.071 (1.010–1.136)	0.022	1.072 (1.012–1.135)	0.018
QRS duration, ms		0.143		0.575
ICD indication	5.387 (1.188–24.430)	0.029		NA
Secondary prevention	12.890 (4.270–38.910)	<0.001	9.092 (2.644–31.258)	<0.001

BNP, brain natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness; NA, not applicable.

Table 3
Summary of the clinical courses of 11 patients with bradyarrhythmia events in the ICD-candidate group.

Sex	Age(at diagnosis)	Acquired ICD indication (after diagnosis)	Bradyarrhythmia event (after diagnosis)	ICD indication	HCM Risk-SCD	Pacing indication	Amiodarone	Beta-blocker	Appropriate shock (after implantation)
Female	71	Concurrently	4 years later	PrimaryNSVT and FH	3.33	SSS	Yes	No	No
Male	57	Concurrently	Within 1 year	SecondarySVT	3.50	SSS	Yes	Yes	Yes10 months later
Female	67	Concurrently	Within 1 year	PrimaryEx-BPR, WT	2.50	SSS	Yes	Yes	No
Female	68	Concurrently	7 years later	SecondarySVT, Syncope	3.60	SSS	Yes	Yes	No
Male	74	Concurrently	Within 1 year	SecondarySVT, Syncope	3.51	SSS	Yes	No	Yes39 months later
Male	84	Concurrently	Within 1 year	SecondarySVT	3.01	AF brady	No	No	No
Male	66	Concurrently	Within 1 year	SecondarySVT	2.74	SSS	No	Yes	Yes45 months later
Female	81	Concurrently	3 years later	PrimaryNSVT	2.59	SSS	No	Yes	No
Female	70	2 years later	2 years later	PrimarySyncope	1.99	SSS	No	Yes	No
Female	84	Concurrently	Within 1 year	SecondarySVT	2.36	SSS	Yes	Yes	Yes2 months later
Female	39	18 years later	19 years later	SecondaryVF	2.94	SSS	Yes	Yes	Yes10 months later

AF brady, atrial fibrillation with a slow ventricular response; Ex-BPR, abnormal exercise blood pressure response; ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia; SSS, sick sinus syndrome, SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; WT, wall thickening (maximal left ventricular wall thickness $\geq$ 30 mm).

they usually require several treatments to ameliorate the symptoms, to stabilize hemodynamics, and to prevent SCD [1,16,17]. In addition, our data suggested that a certain number of patients with HCM, even though the number was small, would be necessary for pacing therapy.

Only a few studies have discussed a bradyarrhythmia risk in HCM patients. In the retrospective study published by Barriales-Villa R et al. [10], 8% of the study population required permanent pacemaker implantation during a median of 5.2 years of observation. This incidence of bradyarrhythmia requiring pacing therapy was similar to that of our study. Besides, a post hoc analysis of the multicenter automatic defibrillator implantation trial (MADIT) II [18] demonstrated that among 458 patients who had eligibility for an ICD implantation but denied the implantation at the enrollment of the trial, 18 patients (4%) required a pacing therapy due to SSS or AVB during 20 months follow-up. Comparing to this incidence of bradyarrhythmia in patients with ICD indications, HCM patients may have a higher incidence when they become eligible for an ICD implantation. According to the study by Fananapazir L et al. [19], which demonstrated several findings of electrophysiological investigations in patients with HCM, prolonged sinoatrial conduction times >120 ms was shown in 66% of the study patients, but only 7% of the patients showed abnormal sinus node recovery times (>1500 ms). Of note, these authors also reported electrophysiological findings in 30 patients with HCM and with experience of an aborted SCD [20]. About half of the patients (n = 14, 47%) showed sinus node dysfunction. In contrast, only 3% of them showed delayed atrioventricular conduction. These data suggest that HCM patients at high risk for SCD may have a potential risk to proceed to symptomatic SSS based on their atrial conduction disturbance. Consistently, in the current study, the patients who were eligible for ICD implantation experienced bradyarrhythmia events due to SSS as a primary cause. Furthermore, our findings, which show that a higher incidence of bradyarrhythmia events in patients with ICD indications than those without, suggested that the common mechanism might be underlying between sinus node dysfunction and ventricular tachyarrhythmia in patients with HCM.

It is well known that amiodarone has bradycardia pharmacological effects and a longer half-life than other anti-arrhythmic drugs or rate control drugs [21], and use of it could worsen bradyarrhythmia. A fibrillation registry assessing costs, therapies, adverse events, and lifestyle (FRACTAL) study [22], which was conducted to assess the relationship of an amiodarone usage to an occurrence of bradyarrhythmia requiring pacemaker implantation in patients with AF, demonstrated that an administration of amiodarone to patients who were pointed out new-onset AF strongly associated with bradyarrhythmia requiring pacing therapy in the future after adjustment for some clinical backgrounds. In contrast, an administration of amiodarone as well as beta-blocker is recommended for HCM patients at risk for SCD despite their bradyarrhythmia risk. Consistently, according to the comparison of prescription, the ICD-candidate group more frequently received both beta-blocker and amiodarone therapies than the non-ICD-candidate group.

Patients with HCM have various atrial or ventricular arrhythmias concomitantly, resulting in hemodynamic deterioration or SCD. The patients with rapid AF, SVT, or VF usually require amiodarone therapy as primary prevention therapy of the arrhythmia [11,17]. Therefore, the risk for bradyarrhythmia increases in HCM patients with ICD indications, especially in patients with experience of SVT or VF who are recommended for amiodarone therapy.

There were several limitations in our study. First, we analyzed data retrospectively in a single institution. The study cohort had a low incidence of new-onset bradyarrhythmia events and a small population. Therefore, we considered that the statistical power of the multivariable Cox proportional-hazards model on our study patients would not be adequate to identify independent predictors of bradyarrhythmia events. In addition, we did not include younger HCM patients (<20 years), because they might be differentiated from the adult patients due to their worse prognosis and higher risk for sudden cardiac death. [23] The limitations of study population might affect the results of this study. Thus, a future prospective study is needed to strengthen our conclusions, with a larger study cohort in which more bradyarrhythmia events would occur. Second, 37% of our study patients showed an apical subtype of HCM, which was a frequent type of HCM for Japanese and characterized as different from that reported by Maron et al [24]. The effect of the study cohort which consisted of patients with an apical subtype of HCM accounted for more than 30% of all on the incidence of bradyarrhythmia in this study should be considered. In addition, LVOT obstruction was observed in only 20% of the patients. Although we could not obtain the data from provocation test such as an exercise stress echocardiography of all study patients due to the nature of the retrospective study, careful evaluation using such a provocation test could have identified dynamic LVOT obstruction in more patients. That may have a possibility to

make the contribution of LVOT obstruction to bradyarrhythmia events lower. Third, we could not obtain the genetic information of study patients because genotype-phenotype correlations in HCM have not been fully elucidated [16] and genetic testing was not generally recommended for patients with HCM in Japan. However, some specific mutations in HCM have been reported to associate with conduction disturbance and/or sick sinus syndrome [25–27]. In future, further studies are needed to confirm the usefulness for risk stratification of future bradyarrhythmia using genetic information. Finally, in the current study, we did not evaluate the association between additional administrations of amiodarone and/or beta-blocker during a follow-up period and bradyarrhythmia events because we could not obtain adequate information of additional administrations of these drugs. This point is critical to conclude whether bradyarrhythmia events in HCM might be occurred by the advanced pathophysiological damage over time or the iatrogenic factors. However, the ICD-candidate group can't avoid the pharmacological bradycardia, because guidelines recommend for HCM patients at risk for fatal ventricular arrhythmia to receive amiodarone and/or beta-blocker therapies.

In conclusion, during 5.5 years after their diagnosis of HCM, 8% of HCM patients suffered from bradyarrhythmia requiring pacing therapy. Our findings suggest that HCM patients, especially those who need ICD implantation for prevention of SCD, need watchful waiting for future bradyarrhythmia requiring pacing therapy. S-ICD implantation in patients with HCM should be careful when considering a future bradyarrhythmia event.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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